EXCOR® Pediatric VAD

Ventricular Assist Device with Stationary Driving Unit Ikus Rev. 2.1

Physician‘s Manual 1000722x03 Revision 4

For products in USA:

Humanitarian Device. Authorized by Federal law for use in the treatment of pediatric patients with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support. The effectiveness of this device for this use has not been demonstrated.

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HOTLINE

Notify Berlin Heart! 866.249.0128

This physician's manual (PM) corresponds to the following product versions:

- Ikus software from V 3.41 forward
- Laptop software from V 3.50 forward
- Laptop from CF30 forward

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Content

Dear readers,

This Physician's Manual (PM) is intended for all medical personnel involved in caring for a patient who is being supported by an EXCOR® Pediatric VAD (referred to as EXCOR in this instruction for use).

The PM provides recommendations on treatment and application of the EXCOR in conjunction with the Stationary Driving Unit Ikus (referred to as Ikus in this PM). To ensure patient safety and comfort, please read this PM carefully.

Always make sure that only professional medical personnel who have been specifically trained in the use of the product are permitted to work with EXCOR.

Note: The recommendations in this PM are based on Berlin Heart's experience with the EXCOR. The decisions related to implantation, the components to be used, and patient care remain with the patient's physicians.

Note: The technical aspects of Ikus are described in the EXCOR® Pediatric VAD Instructions for Use from Rev. 7 (IFU 1000721x08) forward. This PM applies exclusively in connection with the IFU.

The following pictograms and symbols are used in this instruction for use:

DANGER	Indicates a hazardous situation which, if not avoided, **will** result in death or serious injury to the patient.
WARNING	Indicates a hazardous situation which, if not avoided, **could** result in death or serious injury to the patient.
CAUTION	Indicates a hazardous situation which, if not avoided, could result in minor or moderate injury to the patient and/ or damage to the device.
NOTICE	Notes are practices not related to personal injury. Possible damage to the device.
ADVICE	This symbol identifies measures and procedures which have proved useful and successful in conjunction with EXCOR and which we therefore recommend.
HOTLINE	**Notify Berlin Heart! 866.249.0128**

This is the telephone number of the emergency hotline. The hotline desk is in operation 24 hours a day. This number is intended for use by medical personnel and should be used in cases of emergency only.

INSTRUCTION

1. Individual steps of the instructions are numbered in sequential order.

Definition of the used font formates

Description	Meaning
bold, blue	software texts (messages and menus) except in headings and lists
"text"	quotation
<key>	key on the laptop keyboard
<<filler text>>	e.g. if texts in error messages are various
[dimension unit]	dimension units in tables; e.g. [mmHg]

1 Important safety information

NOTE: This chapter omits safety instructions, information and procedures that refer to the Ikus exclusively. Please refer also to the IFU.

1.1 Warnings

⚠ WARNING

Before using EXCOR, read the PM and the IFU carefully.

Only qualified medical personnel trained specifically in the use of the system are permitted to work with EXCOR. Training courses can be arranged with Berlin Heart, Inc. Use by untrained personnel can pose a risk to the patient and the EXCOR.

On the system EXCOR only use components of this system. Never use other components than those delivered by Berlin Heart GmbH/ Berlin Heart Inc.. Otherwise the warranty is no longer valid.

The Ikus and the components of the EXCOR system must not be modified. Otherwise the secure function of the system can not be guaranteed.

The system EXCOR Pediatric and its components are permitted to be used only by prescription of the attending physician.

Unintended use can pose a risk to the patient and the EXCOR.

To ensure the safety of the patient supported with the EXCOR pediatric the patient should be supervised by qualified medical personnel who have been trained on the use of the system.

Do not use the EXCOR if there is any visable damage of the Ikus or any of its components.

If there is any malfunction of the Ikus while the driving unit is connected to the patient, the Ikus must immediately be replaced.

1.1.1 Storage and durability

⚠ WARNING

The expiration date of each EXCOR product is found on the product labels located on both the outer and inner packaging. The pumps, cannulae and accessories must not be used after the expiration date and even not be re-sterilized. Otherwise there is a risk of patient infection.

An EXCOR blood pump may not be used on a patient for more than 1 year. After this it shall be replaced with new products.

1.1.2 Device configurations

WARNING

EXCOR was not designed to be used in combination with other systems, nor do any of the currently granted approvals allow for this. Use by untrained personnel poses a risk to the patient and to the EXCOR.

In univentricular operation: Always connect the driving tube of the blood pump to the red marked connector.

The units may only be operated with the disposable products and accessories specified in this document. Also see section 12.1: Overview: Product range and possible combinations, page 129. Otherwise there is a risk of functional limitation and/or damage to the Ikus. Failure to observe this stipulation will invalidate all warranty agreements by Berlin Heart Inc..

The connection between the connector *External alarm* (Nurse call) and the internal alarm system of the clinic is not failsafe. The use of this feature does not release the user from supervising the *Ikus* and the displayed messages and alarms.

1.1.3 Procedural techniques - Ikus

WARNING

Whenever the Ikus is running in battery operation, the patient must be accompanied by a person trained to use the manual pump. Thus the patient shall be guaranteed care in an emergency.

1.1.4 Packaging and sterilization

WARNING

EXCOR blood pumps and cannulae are intended for single-use only. Otherwise there is a risk of infection.

The sterile components are sterilized using ETO and are packed in a double-layer sterile package. Check that the various layers of the sterile packaging are not damaged in any way before they are opened. Do not use the components if either of the sterile packages are damaged. The same applies to sterile components which have exceeded the expiration date as printed on the label. Otherwise there is a risk that the product is no longer sterile.

EXCOR sterile components may not be resterilized by the user. Any opened product must be used or sent back to Berlin Heart. If product expires please contact Berlin Heart for exchange.

An aluminum-coated external packaging protects the Carmeda® BioActive Surface (CBAS) of the blood pump and its sterile packaging against fluctuations in relative humidity. Do not use blood pumps with damaged external packaging. Otherwise there is a risk that the *CBAS* coating may be compromised.

The following items are delivered in sterile condition: blood pumps, cannulae, cannula extension sets / connecting sets, driving tubes, de-airing set, de-airing hammer, tube connecting set, membrane set.

The external packaging and the outer surface of the outer sterile packaging are not sterile. These 2 packaging layers must be removed before the inner sterile packaging containing the product is handed over to the sterile field. Otherwise there is a risk that the sterile field will be contaminated.

1.1.5 Procedural techniques - pumps, cannulae, accessories

⚠ WARNING

The preparation and use of blood pumps should only be performed by trained personnel. Surgical, nursing and perfusion personnel without experience in the use of EXCOR must complete the EXCOR Training Course which provides theoretical introduction and hands-on practical exercises in the operation of this system. The training program is organized and offered by Berlin Heart, Inc.

Only use sterile components which have been delivered in undamaged sterile condition (sterile packaging intact, expiration date not expired).

Only use blood pumps which have an undamaged aluminum-coated outer packaging.

The long-term storage conditions for all sterile products must be observed: temperature +15°C to 25°C, relative humidity: 35 % to 50 %. Store in a dry place! Otherwise there is a risk that the product is no longer sterile.

In order to prevent infection, use strict aseptic techniques during implantation and exercise extreme caution throughout the period of EXCOR cardiac support. Danger of infection!

The distal end of the cannulae can be trimmed. At least 5 cm (2 inches) of material without polyester velour covering should remain to allow visual inspection of the cannula/ titanium-connector junction. Otherwise there is a risk that possible deposits if formed, cannot be visualized.

Ensure proper placement of the cannulae, especially with respect to orientation of the LV apex cannula, to prevent suction of the myocardial wall.

Prior to initial operation of the blood pump(s) minimal initial start parameters have to be set on the laptop to ensure smooth transition from CPB to VAD support.
When connecting the blood pump(s) to the cannulae always observe the arrows on the inflow and outflow stubs. They show the blood flow direction. There is a risk of injury to the patient and severe pump malfunction if the titanium connectors on the end of the inflow and outflow stubs are not connected to the appropriate cannulae.

Do not touch or manipulate the blood pumps and cannulae with pointed or sharp-edged objects (surgical instruments, wire brushes, etc.). Otherwise there is a risk of blood pump and cannula leakage.

Do not touch or manipulate the drive lines with pointed or sharp-edged objects (surgical instruments, wire brushes, etc.), otherwise these components could be damaged.

Creating a transcutaneous tunnel for the LV apex cannula: Always use cannula tunnelling tip, never use a sharp surgical instrument directly on the cannula.

Cannula extension set and connecting set

⚠ WARNING

If, on *further shortening* of the cannula, visual inspection of the titanium connector on the blood pump is no longer possible: use the cannula extension set.

The cannula extension set and the connecting set should only be used if neccessary, since the basic risk of thrombogenesis and deposits increases each time the cannula is extended.

Do not combine the connecting set with stage cannulae in such a way that multiple diameters are bridged. Otherwise, the pump will not fill or empty completely.

Secure each of the connections with at least 1 cable tie. Otherwise, the connections may loosen over time and the cannula extension set / the connecting set may become separated from the blood pump.

All effort should be made to minimize the manipulation and distortion of the blood pumps and cannula during the removal of the cable tie(s) to prevent mobilization of deposits.

If it is necessary to clamp any other part of the cannula (cannula extension set / connecting set resp.) that is not covered with velour, cover the part that will be clamped with a gauze sponge.

When using a cannula extension set / a connecting set it may be necessary to shorten the respective connecting tube, but the minimum length must be maintained. See Tab. 1-1, page 7.

Article	Diameter / Diameter reduction	Minimum length
Cannula extension set		
A06-006	6 mm	55 mm
A09-009	9 mm	60 mm
A12-012	12 mm	75 mm
Connecting set		
A06-009	9 to 6 mm	60 mm
A09-012	12 to 9 mm	75 mm

Tab. 1-1 Cannula extension set / connecting set: minimum length of tube section

WARNING

Follow exactly the instructions for using the de-airing set. Otherwise there is a risk of membrane damage.

Ensure that cannulae, blood pump(s) and driving tubes are not subject to external forces, like compression, traction or torsion forces, and are free of knots or sharp bends. Prevent the cannulae and connectors from being exposed to tensile forces. Otherwise there is a risk of obstruction of the air and blood flow.

When positioning the driving tubes mitigate the risk of adverse tubing and line incidents by routing the driving tubes in a clear pattern toward the feet and to the side.

Do not initiate cardiac support with the EXCOR blood pumps until the blood pumps have been completely de-aired. After connecting the cannulae, ensure removal of all air that is still in the atria or ventricle by performing single steps (**Step left**, **Step right**) with subsequent removal of the bubbles inside the pump via the de-airing needle. Otherwise there is a risk of embolism.

When removing the de-airing needle, never pull on the de-airing tube, but rather only on the de-airing needle (see also 5.5, page 52).

Once the de-airing needle has been removed it cannot be re-inserted.

Rates < 60 bpm are intended to be used only for implantation and explantation. Never use the Ikus with a rate < 60 bpm without constant supervision.

Secure each connection between blood pump and cannula with at least one cable tie as soon as the proper function of the EXCOR is established (see section 6.12: Securing the connections, page 76). Otherwise there is a risk of loose connections and inadequate blood supply to the patient.

At least every 4 hours, visually check that the blood pump(s) is (are) filling and ejecting completely over a period of several pump cycles. If a pump is not filling and/ or ejecting completely, institute the appropriate corrective action.

Do not kink the drivelines. Otherwise there might not be sufficient pump output.

In no case should the cannulae either be kinked directly at the connector to the blood pump or at the transition area between velour and silicone.

Do not kink the cannulae needlessly. Otherwise there might not be sufficient pump output. Moreover, cannulae might be damaged.

Wound care and treatment: Before cleaning the wound (see section 8.3: Cleaning of the wound, page 83), put on sterile disposable gloves, cap and mask.

Weaning: If the patient does not meet the eligibility criteria at any time during the weaning process: Resume pumping at rate prior to any weaning (initial rate, IR).

1.1.6 System

WARNING

If a non-matching pump-cannula-combination (see section 12.1.6: Overview: Which cannulae should be used for which pump?, page 132) was chosen, use only the connector sets provided with the system in order to minimize the risk of clots at the junctions. Be aware of increased risk of thrombosis and hemolysis.

The cannula diameter may be adapted only once (either by using a staged cannula or a connector set.) Multiple staging could result in limited pump performance and compromised hemodynamics.

If the Ikus is operating in emergency pulse mode, immediately visually check whether the blood pump(s) is (are) filling and ejecting completely. If one pump is not filling and/or ejecting completely, the patient must be supported immediately using the manual pump (see section 10.2: Driving blood pump(s) with the manual pump, page 107). Otherwise there is a risk that the patient will not be supported sufficiently.

1.1.7 Procedures to minimize risk of thrombosis

WARNING

Ensure complete filling/ejection of the pump.

When using staged cannulae or a cannula extension set / connecting set, the pumping rate may not be greater than the respective value found in Tab. 12-9, page 134, as the pump will not eject its full volume at higher rates.

At least every 4 hours, visually check of blood pump(s), visible part of cannulae, cannula extension set and connecting set for deposit formation.

1.1.8 Cleaning the components

WARNING

Cleaning the pump and the drive line: Do not use any acetone or petroleum based products near the pump or drivelines.
We recommend using only water or alcohol to clean the pump and the drive line.
IMPORTANT: Do not use any corrosive or colored solutions or organic solvents to clean the blood pump or drivelines as they may alter the surface of the product.

Cleaning the cannulae and transcutaneous exit site: Do not use any acetone or petroleum based products near the cannulae and the transcutaneous exit site.
We recommend using chlorhexidine to clean the cannulae and transcutaneous exit site.
IMPORTANT: Do not use any corrosive or colored solutions or organic solvents to clean the cannulae and transcutaneous exit site as they may alter the surface of the product.

1.1.9 Errors and corrective measures

WARNING

Any time an error message has occurred, visually check that the blood pump(s) is (are) filling and ejecting completely over a period of several pump cycles, then address the error message with the appropriate corrective action.

In order for a driving tube to be replaced, the pump must be stopped for a short time. If the left driving tube is being replaced in a driving unit providing biventricular support, the right pump must also be stopped while the driving tube is being replaced in order to avoid overloading of the pulmonary circulation (danger of pulmonary edema).

If the left pump is being replaced in a VAD providing biventricular support, the right pump must also be stopped while the pump is being replaced in order to avoid overloading the pulmonary circulation (danger of pulmonary edema).

If the emergency pulse mode is activated while the backup system is already active, the Ikus is no longer able to drive both pumps. In this case the patient must be supported immediately with the replacement Ikus. Use the manual pump while securing the replacement Ikus (see IFU and section 10.2: Driving blood pump(s) with the manual pump, page 107 of this document). Otherwise there is the risk that the patient will not be supported sufficiently.

If the Ikus is operating in emergency pulse mode, the user must immediately visually check the blood pump(s) to determine whether the pump(s) are filling and ejecting completely. If one pump is not filling and/or ejecting completely the patient must be supported immediately with the replacement Ikus. Use the manual pump while securing the replacement Ikus (see IFU and section 10.2: Driving blood pump(s) with the manual pump, page 107 of this document.). Otherwise there is the risk that the patient will not be supported sufficiently.

1.1.10 Replacing the blood pump(s)

WARNING

When replacing a blood pump, follow the instruction given here. Otherwise the duration of the pump stop will be prolonged and the patient might suffer from inadequate support.

The blood pump may only be replaced under sterile conditions!

When connecting the blood pump(s), pay attention to the direction of the arrows on the inflow and outflow stubs! These show the direction of the blood flow.

The cable tie covering the EXCOR cannula on the stub of the blood pump should be removed carefully. Use an appropriate blunt tool. IMPORTANT: never use a sharp instrument, for example, a scalpel or scissors, to remove the cable tie. This may cause damage to the cannula.

If the left pump is being replaced in a VAD providing biventricular support, the right pump must also be stopped while the pump is being replaced in order to avoid overloading the pulmonary circulation (danger of pulmonary edema).

If air or blood collects between any of the layers of the membrane, replace the blood pump. Otherwise, support may be inadequate.

1.1.11 Driving blood pump(s) with the manual pump

WARNING

The use of the manual pump is only permitted for medical personnel trained in the use of it.

Pay attention to the colored markings on the driving tubes and on the connectors of the manual pump. Otherwise, there is a risk of lung edema.

Always keep manual pump attached to the Ikus. Otherwise in an emergency situation the adequate support of the patient is not guaranteed.

Call one or more persons to assist. Otherwise in an emergency situation the adequate support of the patient is not guaranteed.

The driving tubes and cannulae should be arranged in a bend-free position. Otherwise in an emergency situation the adequate support of the patient is not guaranteed.

When operating the manual pump with 1 hand, do not block the valves with your feet (see valve "2" in Fig. 10-2, page 108).

1.1.12 Ambient conditions

WARNING

Protect the Ikus from exposure to moisture and wetness. Never store or operate the Ikus in a damp environment (e.g. bathroom, etc.). Otherwise there is a risk of functional limitation and/or Ikus malfunction.

In terms of electromagnetic compatibility (EMC) the Ikus is subject to special precautions! Avoid exposure to strong electromagnetic radiation (as generated by mobile/cell phones and cordless phones when switched on, electromagnetic security systems etc.), see IFU. Otherwise there is a risk of electromagnetic disturbances and fault-free functioning of the Ikus cannot be guaranteed.

When using a cell phone in the immediate environment of an Ikus in operation please make sure to keep a distance of at least 0.77 m. For further information please refer to IFU.

When using an RFID device in the immediate environment of an *Ikus* in operation please make sure to keep a distance of at least 1 m. For further information please refer to IFU.

If an ambient temperature of +30°C is continuously exceeded during operation, the lifetime of the batteries is reduced. Therefore, a person trained to use the manual pump should always be present in this case. This should ensure patient care in case of emergency.

Use the Ikus as far away as possible from environments containing flammable gases and use extreme caution. Otherwise there is a risk of explosion or gas ignition. The Ikus would be severely limited in function or malfunction altogether as a result of this damage.

Also see IFU.

1.1.13 Interaction with other procedures and therapies

WARNING

The following procedure is not possible: Magnetic resonance imaging

EXCOR patients with prosthetic aortic valves may have increased risk of thromboembolism.

If EXCOR is used in interaction with other procedures and therapies, observe the movement of the membrane to determine whether the blood pump is filling and ejecting completely. If a pump is not filling and/ or ejecting completely, stop the interacting procedure or therapy and institute the appropriate corrective action.

In terms of electromagnetic compatibility (EMC) the Ikus is subject to special precautions! When exposing Ikus to the procedures and therapies listed below please observe EMC regulations given in the IFU.

For the following procedures and therapies, the manufacturer does not expect any harmful interaction with the Ikus due to the general electromagnetic shielding of the device (see IFU). However, these procedures and therapies must only be applied after consultation with the treating physician.
- Radiotherapy
- Nuclear diagnostics / nuclear therapy
- Electro-stimulation therapy
- Therapeutic ultrasonic treatment (e.g. lithotripsy)
- External defibrillation

The following procedures and therapies have been tested in regard to their interaction with the Ikus and no harmful effects were found, however, these procedures and therapies must only be applied after consultation with the treating physician. Additionally the manufacturer does not guarantee that equivalent devices will not interfere.
- Diathermy
- X-rays
- Computed tomography

1.2 Precautions

1.2.1 VAD placement technique

⚠ CAUTION

Implantation - anesthesia: There should be an adequate supply of pre-matched stored blood, fresh frozen plasma and platelet concentrates available for immediate transfusion if required.

Implantation - anesthesia: Keep blood product transfusions to a minimum. Blood transfusions may lead to the development of antibodies, which are known to promote coagulation and inflammatory response.

The titanium connectors of the blood pumps have sharp edges designed to minimise the risk of clot formation at the junction. Be careful to avoid cutting yourself while connecting the pump and the cannulae.

1.2.2 Ambient conditions

CAUTION

The Ikus is intended solely for use in a hospital setting.

Before putting the Ikus into operation, check that the ambient conditions are suitable (see IFU).

1.2.3 Caution while on device support

CAUTION

At least daily, the EXCOR cannulae should be inspected for signs of wear or damage. ADVICE: To avoid needless kinking of the cannulae use a mirror for inspection of the bottom side of the blood pump.

At least every 4 hours, check visually that the blood pump(s) is (are) filling and ejecting completely over a period of several pump cycles. If a pump is not filling and/ or ejecting completely, then take the appropriate corrective action.

Educate the patient, family and caregiver to avoid pulling, kinking or any activity that could put stress on the cannula. Remind them periodically of the importance of protecting the cannnula and blood pump. Do not allow patient to belly flop, pull or stretch the cannula, as this may damage the cannula resulting in injury or death to the patient.

After changing over to biventricular operation the device is operating in separate mode. All parameters are reset to the default parameters (see IFU). The patient-customized parameters have to be adjusted again.

Replacing the blood pump due to growth of the patient: In children, plan to replace the pump(s) with a larger pump(s) in good time, to prevent the possibility of inadequate support due to an insufficient discharge rate.

1.3 Obligations of the operator

WARNING

Only qualified medical personnel trained specifically in the use of the system are permitted to work with EXCOR. Training courses can be arranged with Berlin Heart, Inc.

CAUTION

The operator (i.e. the hospital using the system) is responsible for instruction and care of the patient. The patient must be instructed on safety risks and cautionary measures (moisture, temperature, electromagnetic fields, etc.).

A replacement Ikus and replacement equipment must always be available in the hospital.

2 General Information

2.1 Device description

EXCOR is an extracorporeal, pneumatically driven ventricular assist device. It is designed to support the right and/or left ventricle when the native heart is unable to maintain normal blood flows and pressures even with help of drug therapy and intra-aortic balloon counterpulsation. The device is designed for mid to long term mechanical support.

The EXCOR consists of 1 or 2 extracorporeal, pneumatically driven blood pumps and cannulae which connect the blood pump(s) to the atrium or ventricle and to the great arteries. The Ikus provides alternating air pressure to the blood pumps through driving tubes.

The blood pump is divided into an air chamber and a blood chamber by a multi-layer flexible polyurethane membrane. The alternating air pressure provided by the *Ikus* moves the membrane, thus filling and emptying the blood pump. Both the blood chamber and the polyurethane connectors are transparent to allow for visual detection of deposits and for monitoring the filling and emptying of the blood pump.

Valves (three-leaflet polyurethane valves) are located at the inlet and outlet positions of the blood pump connector stubs, thus ensuring the unidirectional blood flow.

Pulse rate, systolic drive pressure, diastolic suction pressure and the relative systolic duration can all be monitored and adjusted on the driving unit.

2.2 Indications for use

The EXCOR is intended to provide mechanical support as a bridge to cardiac transplantation for pediatric patients. Pediatric patients with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR.

2.3 IDE Clinical Study Summary

See chapter 3: Summary of Clinical Studies, page 17.

2.4 Intended operation environment

Ikus is intended for use in a clinical setting. It can be used in any kind of hospital unit, e.g. OR, ICU, intermediate care unit or general care unit. It may be moved between clinical units using the built-in wheels, however in this case the patient must always be accompanied by a person trained in the use of the manual pump and emergency procedures. Thus, the patient shall be guaranteed care in case of an emergency.

Transporting the device during operation by any vehicles (e.g. ambulance, aircraft, etc.) is not allowed.

During movement of the device in operation within the clinic all electromagnetic compatibility precautions (EMC precautions) must be observed. See IFU. Otherwise there is a risk of electromagnetic disturbances and the fault-free operation of Ikus could not be guaranteed.

2.5 Contraindications

Patients unable to tolerate systemic anticoagulation therapy should not be implanted.

Magnetic Resonance Imaging (MRI) is contraindicated in patients after being implanted with the EXCOR.

Patients with aortic valve regurgitation that is more than moderate that cannot be repaired at the time of implantation should not be implanted with the EXCOR. If repair of the aortic valve regurgitation requires surgical closure of the aortic valve, the EXCOR should not be implanted. The EXCOR is not intended to be used as a total artificial heart and should not be used in this configuration.

2.6 Storage and durability

WARNING

The expiration date of each EXCOR product is found on the product labels located on both the outer and inner packaging. The pumps, cannulae and accessories must not be used after the expiration date and even not be re-sterilized. Otherwise there is a risk of patient infection.

An EXCOR blood pump may not be used on a patient for more than 1 year. After this it shall be replaced with new products.

IMPORTANT: EXCOR must be stored at room temperature and be protected against extreme temperature fluctuations and moisture. Otherwise there is a risk of functional limitation and/or damage to the Ikus.

3 Summary of Clinical Studies

3.1 Indications for use

EXCOR® Pediatric Ventricular Assist Device (referred to as EXCOR) is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR.

3.2 Contraindications

Patients unable to tolerate systemic anticoagulation therapy should not be implanted.

Magnetic Resonance Imaging (MRI) is contraindicated in patients after being implanted with the EXCOR.

3.3 Alternative Practices or Procedures

FDA approved therapies include the Debakey Child device for left ventricular support for body surface area > 0.7 m2 and < 1.5 m2. EXCOR is the only ventricular assist device approved for univentricular and biventricular support in children from 3-60 kg.

3.4 Marketing History

EXCOR was approved to apply the CE Mark in 1996. Since that authorization, EXCOR has been distributed to the following countries: Germany, Austria, Belgium, Bulgaria, Estonia, Switzerland, Denmark, Spain, Finland, France, Great Britain, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Romania, Sweden, Slovakia, Turkey, Argentina, Australia, Azerbaijan, Brazil, Canada, Chile, Taiwan, China, Hong Kong, Israel, Iran, New Zealand, Serbia, Russia, Saudi Arabia, and South Africa. The EXCOR has not been removed from the market in any country.

3.5 Potential Adverse Effects

Serious adverse events (SAEs) for all primary cohort patients were reported in the primary study analysis for events per patient-day. The total time on device for Cohort 1 (BSA <0.7 m2) subjects of 1411 days yielded a rate of 0.068 SAEs per patient-day. The total time on device for Cohort 2 (BSA >0.7 to < 1.5 m2) subjects was 1376 days yielded a rate of 0.079 SAEs per patient-day.

The following table details each SAE with the number of events experienced and the number and percent of subjects experiencing each SAE. Some of the SAEs have subcategories (see indented descriptions) which provide additional detail regarding the type of SAE.

Rates for subjects enrolled in the Cohorts 1 CAP (Continued Access Protocol which allowed continued access to the device following the conclusion of enrollment in the primary cohorts) and Compassionate/ Emergency Use Cohorts 3A and 3B are included to support the assessment of reasonable assurance of safety as specified in the IDE Investigational Plan.

Serious Adverse Event Summary per Cohort

EVENT	COHORT								
	1 Total	Per Subject (% of 24)	1 CAP Total	Per Subject (% of 20)	3A Total	Per Subject (% of 35)	2 Total	Per Subject (% of 24)	3B Total	Per Subject (% of 6)
Major Bleeding	**15**	**10 (41.7%)**	**12**	**7 (35.0%)**	**25**	**18 (51.4%)**	**22**	**12 (50.0%)**	**3**	**3 (50.0%)**
Cardiac Arrhythmia	**1**	**1 (4.2%)**	**2**	**2 (10.0%)**	**3**	**3 (8.6%)**	**6**	**4 (16.7%)**	**2**	**1 (16.7%)**
Sustained VT	1	1 (4.2%)	0	0 (0.0%)	2	2 (5.7%)	2	2 (8.3%)	2	1 (16.7%)
Sustained SVT	0	0 (0.0%)	2	2 (10.0%)	1	1 (2.9%)	4	3 (12.5%)	0	0 (0.0%)
Pericardial Fluid Collection	**3**	**3 (12.5%)**	**5**	**5 (25.0%)**	**4**	**4 (11.4%)**	**4**	**3 (12.5%)**	**1**	**1 (16.7%)**
With Tamponade	1	1 (4.2%)	3	3 (15.0%)	2	2 (5.7%)	2	2 (8.3%)	0	0 (0.0%)
Without Tamponade	2	2 (8.3%)	2	2 (10.0%)	2	2 (5.7%)	2	2 (8.3%)	1	1 (16.7%)
Hemolysis	**1**	**1 (4.2%)**	**1**	**1 (5.0%)**	**1**	**1 (2.9%)**	**1**	**1 (4.2%)**	**1**	**1 (16.7%)**
Hemolysis-Early	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (16.7%)
Hemolysis-Late	1	1 (4.2%)	1	1 (5.0%)	1	1 (2.9%)	1	1 (4.2%)	0	0 (0.0%)
Hepatic Dysfunction	1	1 (4.2%)	0	0 (0.0%)	6	5 (14.3%)	1	1 (4.2%)	3	2 (33.3%)
Hypertension	12	12 (50.0%)	15	13 (65.0%)	9	9 (25.7%)	8	8 (33.3%)	1	1 (16.7%)
Major Infection	**35**	**15 (62.5%)**	**15**	**7 (35.0%)**	**39**	**16 (45.7%)**	**24**	**12 (50.0%)**	**8**	**4 (66.7%)**
Infection-Localized Non-Device	25	12 (50.0%)	10	6 (30.0%)	20	11 (31.4%)	18	10 (41.7%)	7	3 (50.0%)
Infection-Percutaneous Site or Pocket	4	4 (16.7%)	1	1 (5.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Infection-Sepsis	6	5 (20.8%)	4	2 (10.0%)	19	9 (25.7%)	6	6 (25.0%)	1	1 (16.7%)
Psychiatric Episode	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (4.2%)**	**0**	**0 (0.0%)**

Tab. 3-1 Serious adverse event summary per cohort

Serious Adverse Event Summary per Cohort, *continued*

EVENT	COHORT											
	1 Total	Per Subject (% of 24)	1 CAP Total	Per Subject (% of 20)	3A Total	Per Subject (% of 35)	2 Total	Per Subject (% of 24)	3B Total	Per Subject (% of 6)
Neurological Dysfunction	8	7 (29.2%)	6	5 (25.0%)	6	6 (17.1%)	9	7 (29.2%)	4	3 (50.0%)
TIA	0	0 (0.0%)	1	1 (5.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (16.7%)
Ischemic CVA	8	7 (29.2%)	5	5 (25.0%)	4	4 (11.4%)	7	7 (29.2%)	3	3 (50.0%)
Hemorrhagic CVA	0	0 (0.0%)	0	0 (0.0%)	2	2 (5.7%)	2	2 (8.3%)	0	0 (0.0%)
Renal Dysfunction	**3**	**2 (8.3%)**	**0**	**0 (0.0%)**	**7**	**7 (20.0%)**	**4**	**3 (12.5%)**	**2**	**1 (16.7%)**
Acute	3	2 (8.3%)	0	0 (0.0%)	7	7 (20.0%)	2	2 (8.3%)	2	1 (16.7%)
Chronic	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	2	2 (8.3%)	0	0 (0.0%)
Respiratory Failure	**3**	**3 (12.5%)**	**8**	**8 (40.0%)**	**6**	**5 (14.3%)**	**9**	**6 (25.0%)**	**6**	**5 (83.3%)**
Right Heart Failure	**2**	**2 (8.3%)**	**2**	**2 (10.0%)**	**8**	**7 (20.0%)**	**3**	**3 (12.5%)**	**1**	**1 (16.7%)**
Arterial Non-CNS Thromboembolism	**1**	**1 (4.2%)**	**1**	**1 (5.0%)**	**2**	**2 (5.7%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Venous Thromboembolism Event	**1**	**1 (4.2%)**	**1**	**1 (5.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Wound Dehiscence	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (2.9%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Other	**10**	**6 (25.0%)**	**6**	**5 (25.0%)**	**17**	**12 (34.3%)**	**15**	**6 (25.0%)**	**7**	**4 (66.7%)**
Other Ischemic w/o symptoms	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (2.9%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Other Covert Stroke	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (16.7%)**

Tab. 3-2 Serious adverse event summary per cohort (table continued)

The rates of SAEs per patient-day were calculated separated by whether the subjects were supported with ECMO pre-implant and are summarized in the following table.

In Cohort 1, those supported with ECMO pre-implant had twice as many events per patient-day of support. For Cohort 2, those supported with ECMO pre-implant had 1.5 times as many events per patient-day of support.

Serious Adverse Events per Patient-day by pre-implant ECMO

Group	ECMO Pre-Implant	# Events	Total Time on Support (Days)	Rates Success Criterion <0.25	
				Events per Patient-Day	Upper bound of CI
Cohort 1	Yes	38	345	0.110	0.151
	No	58	1066	0.054	0.070
Cohort 2	Yes	43	450	0.096	0.129
	No	64	926	0.069	0.088

Tab. 3-3 Serious adverse events per patient-day pre-implant ECMO

3.6 IDE Clinical Study

3.6.1 IDE Clinical Study Summary

Berlin Heart Inc. conducted a prospective, multi-center, single arm study to assess the safety and probable benefit of the EXCOR.

The purpose of the study was to determine whether use of the EXCOR for bridge-to-transplantation is associated with reasonable assurance of safety and probable benefit such that the EXCOR merits approval by the Food and Drug Administration (FDA) under a Humanitarian Device Exemption (HDE).

3.6.2 Study Cohorts

The primary study population of 48 subjects aged 0-16 years consisted of 24 subjects with a body surface area (BSA) < 0.7 m2 (Cohort 1) and 24 subjects with a body surface area (BSA) ³ 0.7 m2 to < 1.5 m2 (Cohort 2).

A third cohort of subjects was enrolled under Compassionate / Emergency Use regulations and is classified as Cohort 3. These subjects followed the study protocol unless otherwise noted within the approval documentation for the subject. This cohort is further divided into groups based on the subject's BSA similar to Cohorts 1 and 2 and is labeled Cohort 3A if the subject's BSA is < 0.7 m2 and Cohort 3B if the BSA is ³ 0.7 m2 and <1.5 m2.

For the primary effectiveness endpoint, the protocol prescribed an ECMO historical control group. The historical ECMO control group was compiled from the Extracorporeal Life Support Organization (ELSO) registry, the most extensive registry of patients treated with ECMO in North America. The database was filtered to best match the EXCOR IDE study population. Patients included for comparison to the EXCOR cohorts included patients from both genders, age 0-16 years, with weight greater than 3 kg, cardiac only ECMO support, support initiation from 2000 onward

who met critical eligibility criteria. The dataset for the ELSO registry included baseline and outcomes data comparable to the EXCOR dataset. The control group was then created by matching the EXCOR subjects to the patients in the subset using a propensity score analysis (PSA).

3.6.3 Inclusion/Exclusion Criteria

Subjects of both genders who satisfy all inclusion and exclusion criteria were eligible for entrance into the primary cohorts of the clinical study.

Inclusion Criteria

1. Severe NYHA Functional Class IV (or Ross Functional Class IV for subjects ≤ 6 years) heart failure refractory to optimal medical therapy, and has met at least one of the following criteria:
    a. INTERMACS™ profile status 1 or 1A, i.e. critical cardiogenic shock (low BP unresponsive to support, compromised end organ perfusion, < 24 hour survival expected without mechanical support; may be due to VT/VF (1A)
    b. INTERMACS profile status 2 or 2A (i.e. progressive decline): not in imminent danger, but worsening despite optimal inotropic therapy; may be due to VT/ VF (2A) AND at least one of the following criteria:
        a. Decline in renal function as defined by a 50 % reduction in estimated GFR despite optimization of subject volume status
        b. Decline in nutritional status as defined by a sustained (≥ 7 days) inability to tolerate an enteral nutritional intake sufficient to provide at least 75 % of the prescribed caloric needs for the subject, or signs of nutritional compromise (cachexia, nutritional weight loss) despite appropriate intervention
        c. Decline in mobility/ambulation as defined by sustained bed confinement (≥ 7 days without prospect for improvement) attributable to heart failure symptoms or its treatment (e.g. intubation for pulmonary edema)
    c. Support with extra-corporeal membrane oxygenation (ECMO) or other mechanical circulatory support device OR
    d. Unable to separate from cardiopulmonary bypass (must be listed for heart transplantation at time of transfer to the operating room)
2. Listed (UNOS status 1A or equivalent) for cardiac transplantation
3. Two-ventricle circulation, including cardiomyopathy, repaired structural heart disease (e.g. ALCAPA, aortic stenosis) or acquired heart disease (e.g. myocarditis, Kawasaki disease)
4. Age 0 to 16 years; corrected gestational (CGA) at least 37 weeks
5. Weight ≥ 3 kg and ≤ 60 kg
6. Legal guardian (and subject if age-appropriate) understands the nature of the procedure, are willing to comply with associated follow-up evaluations, and provide written informed consent and assent prior to the procedure

Exclusion Criteria

1. Support on ECMO for ≥ 10 days
2. Cardiopulmonary resuscitation (CPR) duration ≥ 30 minutes within 48 hours prior to device implantation
3. Body weight < 3.0 kg or BSA > 1.5 m^2
4. Presence of mechanical aortic valve
5. Unfavorable or technically-challenging cardiac anatomy including single ventricle lesions, complex heterotaxy, and restrictive cardiomyopathy
6. Evidence of intrinsic hepatic disease as defined by a total bilirubin level or AST/ALT greater than five times the upper limit of normal for age, except in association with acute heart failure as determined by the principal investigator
7. Evidence of intrinsic renal disease as defined by a serum creatinine greater than 3 times the upper limit of normal for age, except in association with acute heart failure as determined by the principal investigator
8. Hemodialysis or peritoneal dialysis (not including dialysis or Continuous Veno-Venous Hemofiltration (CVVH) for volume removal
9. Evidence of intrinsic pulmonary disease (e.g. chronic lung disease, RDS) as defined by need for chronic mechanical ventilation, except in association with acute heart failure as determined by the principal investigator
10. Moderate or severe aortic and/or pulmonic valve insufficiency considered technically challenging to repair at the time of the device implantation as determined by the principal investigator
11. Apical VSD or other hemodynamically-significant lesion considered technically challenging to repair at the time of device implantation as determined by the principal investigator
12. Documented heparin induced thrombocytopenia (HIT) or idiopathic thrombocytopenia purpura (ITP) or other contraindication to anticoagulant/antiplatelet therapy
13. Documented coagulopathy (e.g. Factor VIII deficiency, disseminated intravascular coagulation) or thrombophilic disorder (e.g. Factor V Leiden mutation)
14. Hematologic disorder causing fragility of blood cells or hemolysis (e.g. sickle cell disease)
15. Active infection within 48 hours of implant demonstrated by:
    a. Positive blood culture OR
    b. Temperature >38 degrees C and WBC >15, 000/ ml
16. Documented human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)
17. Evidence of recent or life-limiting malignant disease
18. Stroke within past 30 days prior to enrollment, or congenital CNS malformation syndrome associated with increased risk of bleeding (e.g. arteriovenous malformation, moya moya)
19. Psychiatric or behavioral disease (e.g. antisocial disorder) with a high likelihood for non-compliance
20. Currently participating in another investigational device or drug trial and has not completed the required follow-up period for that study
21. Subject is pregnant or nursing

3.6.4 Study Enrollment

The following table summarizes the complete enrollment (including the subjects enrolled at non IDE sites) by subject's body size. As of the data cutoff for the final HDE report (February 2011 report with January 17, 2011 data cutoff), there were 151

smaller sized subjects (BSA < 0.7m^2) enrolled and 53 larger sized subjects (BSA ≥ 0.7 to <1.5 m^2) enrolled.

Subject Enrollment

Cohort	IDE Site Implants	Non-IDE Site Implants	Total
BSA < 0.7 m^2			
Cohort 1	24	*n/a*	24
Cohort 1 CAP	20	*n/a*	20
Cohort 3A	35	72	107
Subtotal	*79*	*72*	*151*
BSA ≥ 0.7 m^2 to < 1.5 m^2			
Cohort 2	24	*n/a*	24
Cohort 3B	6	23	29
Subtotal	*30*	*23*	*53*
TOTAL	**109**	**95**	**204**

Tab. 3-4 Subject enrollment

Note: Enrollment in Cohorts 1 CAP, 3A, 3B (IDE and non-IDE) are supportive data and are included only in the safety summary tables.

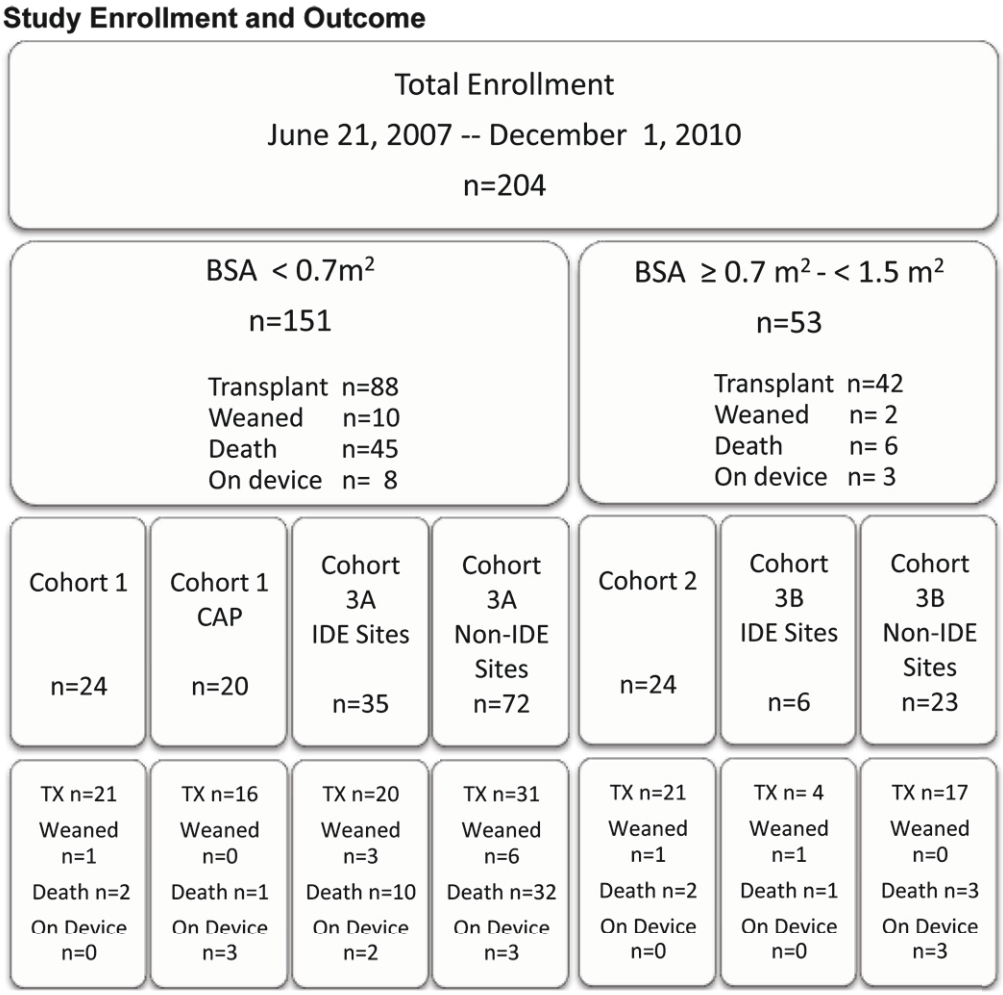


Fig. 3-1 Study enrollment and outcome

Enrollment in Cohorts 1 CAP, 3A, 3B (IDE and non-IDE) are supportive data and are only included in the safety summary tables.

3.6.5 Subject Demographics

The following table summarizes the demographic data for Cohorts 1 and 2. Males comprised the majority of the subjects in Cohort 2 (54%) and half (50%) of Cohort 1. The smaller group of subjects ranged in age from 2.6 to 45.6 months while the larger group ranged in age from 51 to 192 months (or 4.2 to 16 years). The weight range for Cohort 1 was 3.6 to 13.6 kilograms with a BSA range of 0.23 to 0.62 m^2 and the weight range for Cohort 2 was 16.0 to 58.1 kilograms with a BSA range of 0.71 to 1.66 m^2.

The most predominant cardiac diagnosis for Cohort 1 was dilated cardiomyopathy (79.2%) and the majority of this group, 54.2%, presented with progressive decline. The most predominant cardiac diagnosis for Cohort 2 was also dilated cardiomyopathy (70.8%) and most (54.2%) were listed as in critical cardiogenic shock.

Demographic Data Summary

Variable	Category	Cohort 1 n=24	Cohort 2 n=24
Gender	Female	12 (50.0%)	11 (45.8%)
	Male	12 (50.0%)	13 (54.2%)
Age (months)	Mean ± Std (N) Median Min – Max	15.4 ± 12.4 (24) 11.7 2.6 - 45.6	113.2 ± 37.6 (24) 111.2 50.8 - 191.8
BSA (m^2)	Mean ± Std (N) Median Min – Max	0.43 ± 0.10 (24) 0.44 0.23 - 0.62	1.09 ± 0.29 (24) 1.08 0.71 - 1.66
Weight (kg)	Mean ± Std (N) Median Min – Max	9.1 ± 2.7 (24) 9.2 3.6 - 13.6	32.2 ± 12.5 (24) 30.7 16.0 – 58.1
Race	African-American	7 (29.2%)	6 (25.0%)
	American Indian/Alaska Native	1 (4.2%)	0 (0.0%)
	Asian	0 (0.0%)	1 (4.2%)
	Hawaiian/other Pacific Islander	0 (0.0%)	1 (4.2%)
	White	13 (54.2%)	15 (62.5%)
	Other/none of the above	3 (12.5%)	1 (4.2%)
Ethnicity: Hispanic or Latino	Yes	7 (29.2%)	1 (4.2%)

Tab. 3-5 Demographic data summary (a)

Demographic Data Summary, *continued*

Variable	Category	Cohort 1 n=24	Cohort 2 n=24
Patient Profile/Status	1 Critical Cardiogenic Shock	11 (45.8%)	13 (54.2%)
	2 Progressive decline	13 (54.2%)	11 (45.8%)
	3 Stable but Inotrope dependent	0 (0.0%)	0 (0.0%)
Modifier A Arrhythmia (# Yes)		4 (16.7%)	4 (16.7%)
Primary Cardiac Diagnosis	Congenital Heart Disease	3 (12.5%)	6 (25.0%)
	Dilated Myopathy	19 (79.2%)	17 (70.8%)
	Hypertrophic cardiomyopathy	1 (4.2%)	0 (0.0%)
	Restrictive Myopathy	1 (4.2%)	1 (4.2%)
Secondary Cardiac Diagnosis (multiple Choices)	Congenital Heart Disease	2 (8.3%)	3 (12.5%)
	Coronary Artery Disease	0 (0.0%)	2 (8.3%)
	Dilated Myopathy: Familial	1 (4.2%)	0 (0.0%)
	Dilated Myopathy: Idiopathic	0 (0.0%)	2 (8.3%)
	Dilated Myopathy: Ischemic	0 (0.0%)	1 (4.2%)
	Dilated Myopathy: Myocarditis	0 (0.0%)	2 (8.3%)
	Dilated Myopathy: Viral	1 (4.2%)	0 (0.0%)
	Dilated Myopathy: Other	1 (4.2%)	2 (8.3%)
	Restrict Myopathy: Secondary to Radiation/Chemo	0 (0.0%)	1 (4.2%)
	Valvular Heart Disease	0 (0.0%)	1 (4.2%)
	CHD/Dilated Myopathy Familial	1 (4.2%)	0 (0.0%)
	None	18 (75.0%)	10 (41.7%)
Heart Rate	Mean ± Std (N) Min – Max	126.3 ± 25.5 (24) 91.0 - 175.0	117.9 ± 21.1 (24) 85.0 - 168.0
Systolic Blood Pressure	Mean ± Std (N) Min – Max	85.3 ± 16.0 (24) 45.0 - 110.0	95.2 ± 13.5 (24) 60.0 - 112.0
Diastolic Blood Pressure	Mean ± Std (N) Min – Max	56.0 ± 14.1 (24) 38.0 - 89.0	65.9 ± 14.8 (24) 46.0 - 100.0
Previous Cardiac operations (# Yes)		5 (20.8%)	8 (33.3%)

Tab. 3-6 Demographic data summary (b)

Pre-implant support for the subjects is detailed in the following table. ECMO support was used pre-implant for 25% of Cohort 1 subjects and 33.3% of Cohort 2 subjects.

Pre-Implant Support

Variable	Category	Cohort 1 n=24	Cohort 2 n=24
Prior support within 48 hours	No support	0 (0.0%)	0 (0.0%)
	Ventilator	20 (83.3%)	12 (50.0%)
	ECMO	6 (25.0%)	8 (33.3%)
	Ultrafiltration	3 (12.5%)	1 (4.2%)
	VAD	2 (8.3%)	0 (0.0%)
	Dialysis	0 (0.0%)	0 (0.0%)
	Feeding Tube	10 (41.7%)	7 (29.2%)
	IABP	0 (0.0%)	0 (0.0%)
	Inotropes	22 (91.7%)	21 (87.5%)

Tab. 3-7 Pre-implant support

3.6.6 Results

3.6.6.1 Probable Benefit

Efficacy for the IDE trial was assessed by comparing survival (defined by the interval of time from initiation of mechanical support as a bridge to transplant or recovery) to the historical ECMO control. Subjects who were transplanted were censored at the time of explant. Subjects who were explanted due to recovery of their ventricular function and survived to 30 days or discharged with acceptable neurologic status were censored at the time of explant. Subjects who were explanted due to recovery of their ventricular function and died within 30 days or discharge (whichever was longer) were counted as a failure with time to failure being the explant date.

For the 2 primary cohorts, the rate of successfully bridging the subjects to transplant was 87.5% for Cohort 1 (21/24) and 91.7% for Cohort 2 (22/24) or 89.6% overall (43/48). The following table summarizes the survival to transplant/successful recovery for each primary Cohort ITT and PP as well as their matched ECMO control groups.

Three (3) of the Cohort 1 subjects (12.5%) failed (2 deaths and 1 weaned subject with unacceptable neurological outcome at 30 days post-explantation) compared to 12 of the 48 (25%) patients in the matched ECMO control group. The 3 subjects from Cohort 1 who died or were considered failures were all supported with ECMO at the time of implant. The failures occurred at day 0 (death), day 38 (death) and day 146 (weaned-failure).

The control group for Cohort 1 was on ECMO for a median of 4.9 days and a maximum of 20.5 days compared to the primary cohort subjects who were supported a median of 27.5 days and maximum of 174 days. Seventeen (17) of the 24 (71%) Cohort 1 subjects were supported longer than the entire ECMO control group (i.e. longer than 20.5 days).

Two of the Cohort 2 subjects (8.3%) failed compared to 16 of the 48 (33.3%) patients in the matched ECMO control group. One of the subjects who died in Cohort 2 was

supported with ECMO at the time of implant. The deaths occurred at day 19 and day 144.

The control group for Cohort 2 was on ECMO for a median of 4.7 days and a maximum of27.5 days compared to the primary cohort subjects who were supported a median of 42.5 days and a maximum of 192 days. Seventeen(17) of the 24 (71%) subjects in Cohort 2 were supported longer than the entire ECMO control group (i.e. longer than 27.5 days).

Primary Efficacy Study and Control Groups

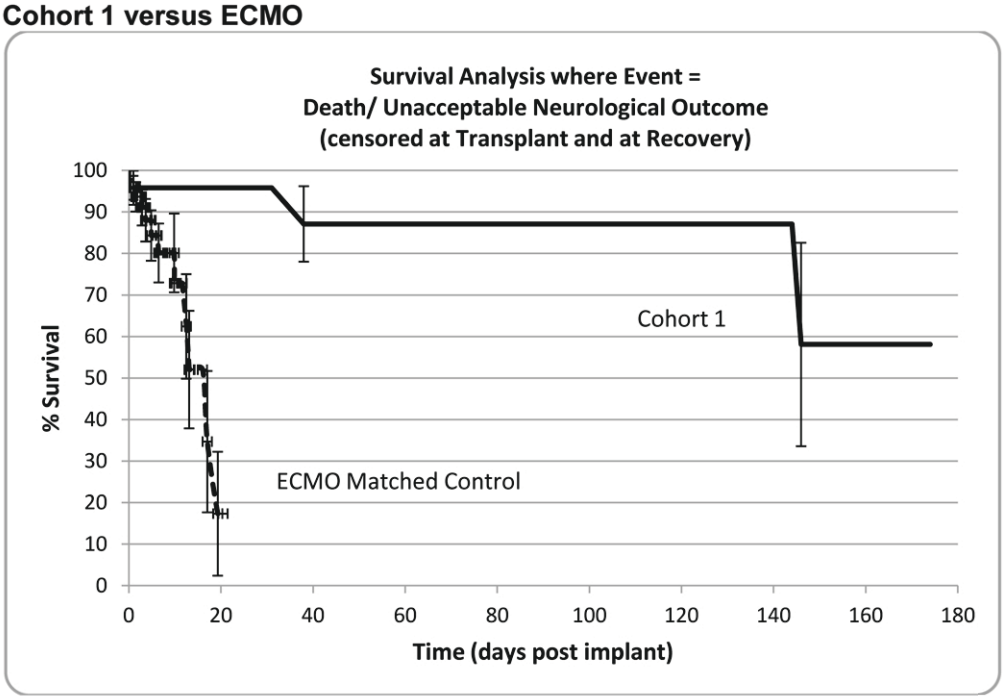
Group	Total	Max Time on Device (days)	# Successes	# Failures	Survival Time		
					30 days	60 days	90 days
Cohort 1 ITT	24	174	21 (87.5%)	3 (12.5%)	95.8%	87.1%	87.1%
Cohort 1 Per-Protocol	22	174	19 (86.4%)	3 (13.6%)	95.5%	86.8%	86.8%
ECMO Control Group	48	20.5	36 (75.0%)	12 (25.0%)	NA	NA	NA
Cohort 2 ITT	24	192	22 (91.7%)	2 (8.3%)	94.7%	94.7%	94.7%
Cohort 2 Per-Protocol	22	144	20 (90.9%)	2 (9.1%)	94.1%	94.1%	94.1%
ECMO Control Group	48	27.5	32 (66.7%)	16 (33.3%)	NA	NA	NA

Tab. 3-8 Primary Efficiacy Study and Control Groups

Comparison of the ITT groups to their respective matched ECMO control group survival rates were both statistically significant (log-rank p value <0.0001). Therefore, there is a significantly higher survival rate of Cohort 1 and 2 subjects as compared to their respective ECMO control group.

The following figures display the Kaplan-Meier curves for the endpoint of death/ weaned with unacceptable outcome for both Cohort 1 ITT and Cohort 2 ITT and their respective ECMO control groups.

Survival to Death/Weaned with Unacceptable Neurological Outcome: Cohort 1 versus ECMO

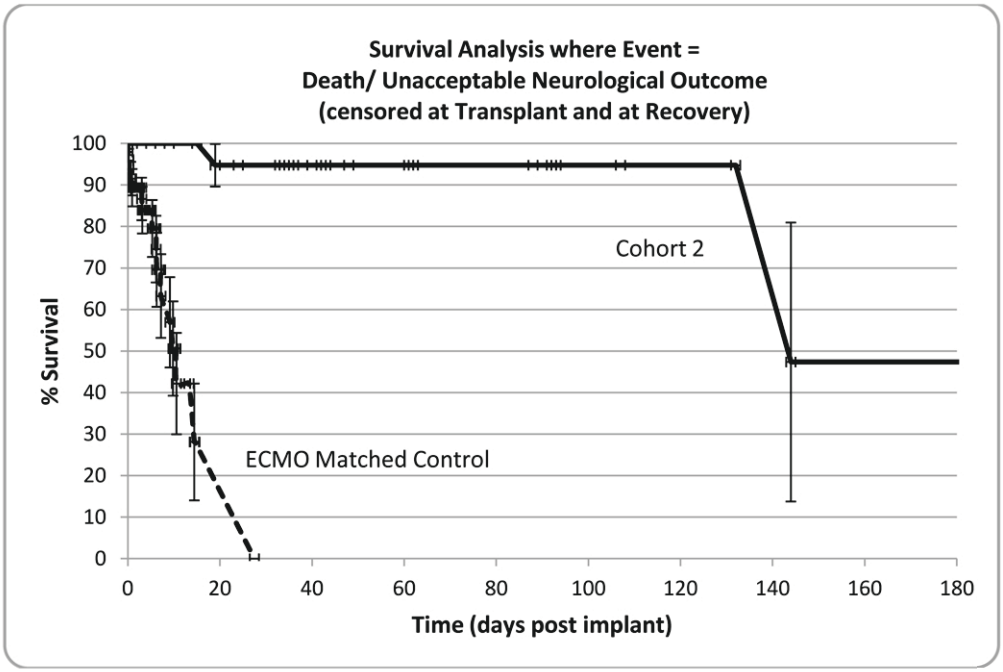


	Interval Ending (Days Post Implant)									
COHORT 1	**0**	**1**	**7**	**14**	**30**	**45**	**60**	**90**	**120**	**150**
# Left	24	21	21	20	12	10	9	6	5	1
Total # Failed	0	1	1	1	1	2	2	2	2	3
Survival	100%	95.8%	95.8%	95.8%	95.8%	87.1%	87.1%	87.1%	87.1%	58.1%
Std Error	0%	4.1%	4.1%	4.1%	4.1%	9.1%	9.1%	9.1%	9.1%	24.5%

	Interval Ending (Days Post Implant)					
ECMO CONTROL	**0**	**1**	**7**	**14**	**30**	
# Left	48	46	16	4	0	
Total # Failed	0	2	7	10	12	
Survival	100%	95.8%	80.1%	52.0%	17.3%	
Std Error	0%	2.9%	7.1%	14.2%	14.9%	

Fig. 3-2 Cohort 1 Survival

Survival to Death/Weaned with Unacceptable Neurological Outcome: Cohort 2 versus ECMO



COHORT 2	Interval Ending (Days Post Implant)									
	0	1	7	14	30	45	60	90	120	150
# Left	24	23	21	20	17	11	9	6	3	1
Total # Failed	0	0	0	0	1	1	1	1	1	2
Survival	100%	100%	100%	100%	94.7%	94.7%	94.7%	94.7%	94.7%	47.4%
Std Error	0%	0%	0%	0%	5.1%	5.1%	5.1%	5.1%	5.1%	33.6%

ECMO CONTROL	Interval Ending (Days Post Implant)					
	0	1	7	14	30	
# Left	48	41	12	3	0	
Total # Failed	0	5	10	15	16	
Survival	100%	89.4%	69.6%	42.2%	0%	
Std Error	0%	4.5%	8.9%	12.2%	.	

Fig. 3-3 Cohort 2 Survival

Because the Kaplan-Meier analysis censors subjects at time of transplant, “Competing Outcomes” curves were constructed to show a more complete picture of the endpoints.

The following figure shows the “Competing Outcomes” for Cohort 1. The curves represent each of the outcomes and at any time point the sum of the proportions of outcomes equals 100%.

Of the 24 Cohort 1 subjects, 21 were transplanted between 1 to 174 days of support. The 2 deaths in this Cohort occurred at 0 and 38 days post implant. One subject was weaned after 146 days due to poor prognosis.

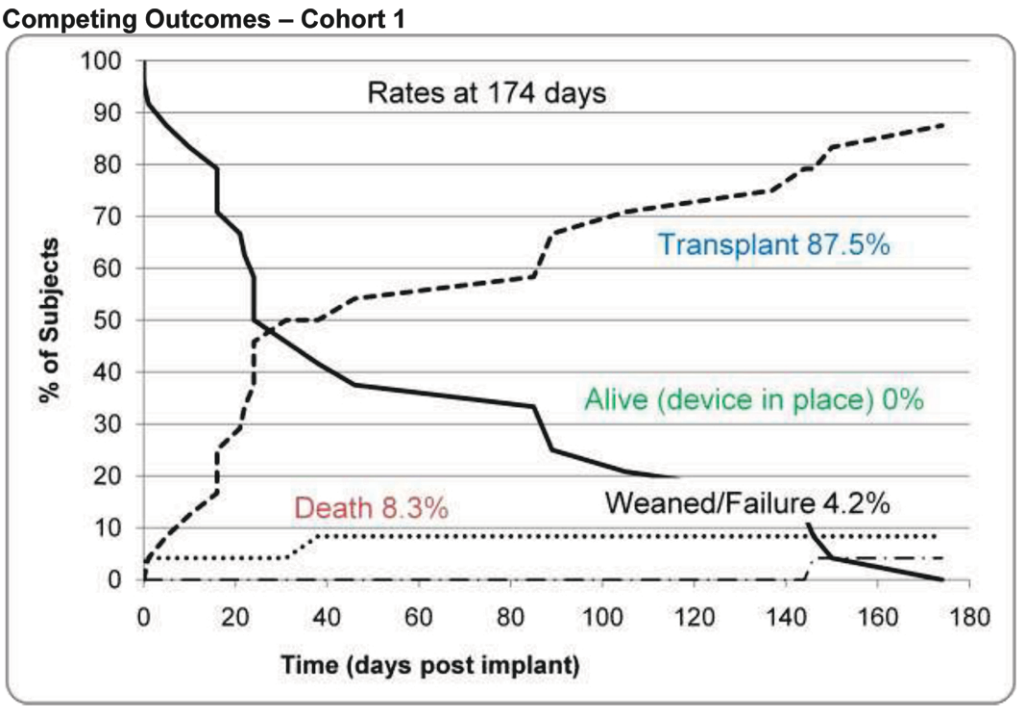


Fig. 3-4 Cohort 1 Competing outcomes

The next figure shows the “Competing Outcomes” for the ECMO control group for Cohort 1. The longest support time was 20.5 days at which time 75% were weaned from ECMO for recovery or transplant.

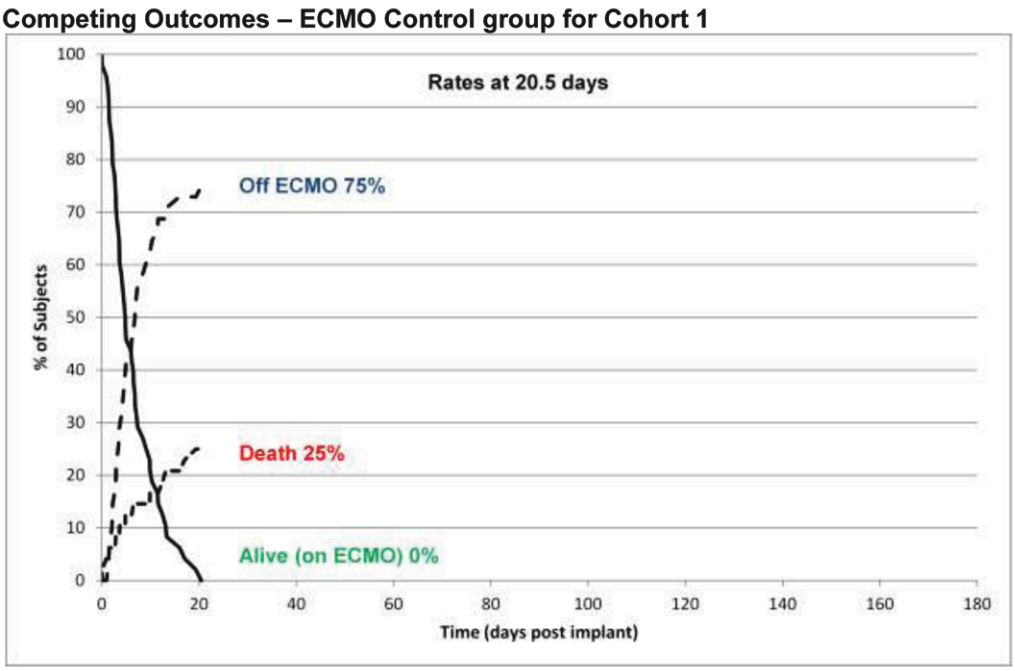


Fig. 3-5 Cohort 1 control group competing outcomes

The following figure shows the “Competing Outcomes” for Cohort 2. Of the 24 Cohort 2 subjects, 21 were transplanted between 3 to 192 days of support. The 2 deaths in

this Cohort occurred at 19 and 144 days post implant. One subject was successfully weaned to recovery after 9 days.

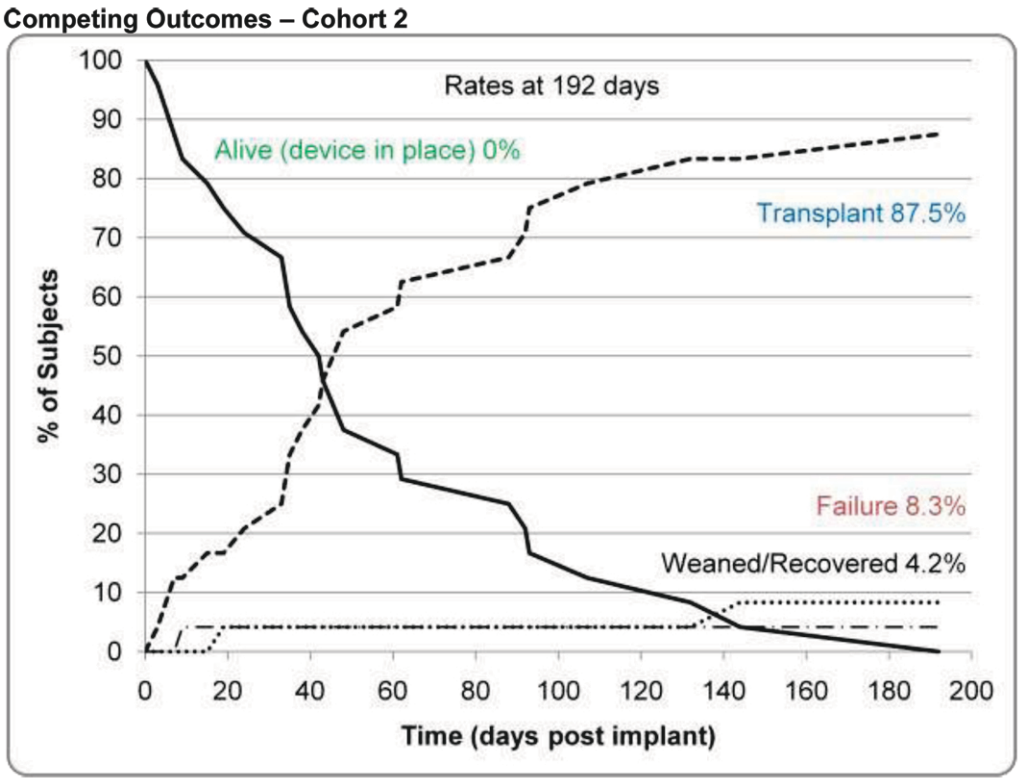


Fig. 3-6 Cohort 2 competing outcomes

The next figure shows the “Competing Outcomes” for the ECMO control group for Cohort 2. The longest support time was 27.5 days at which time 67% were weaned from ECMO for recovery or transplant.

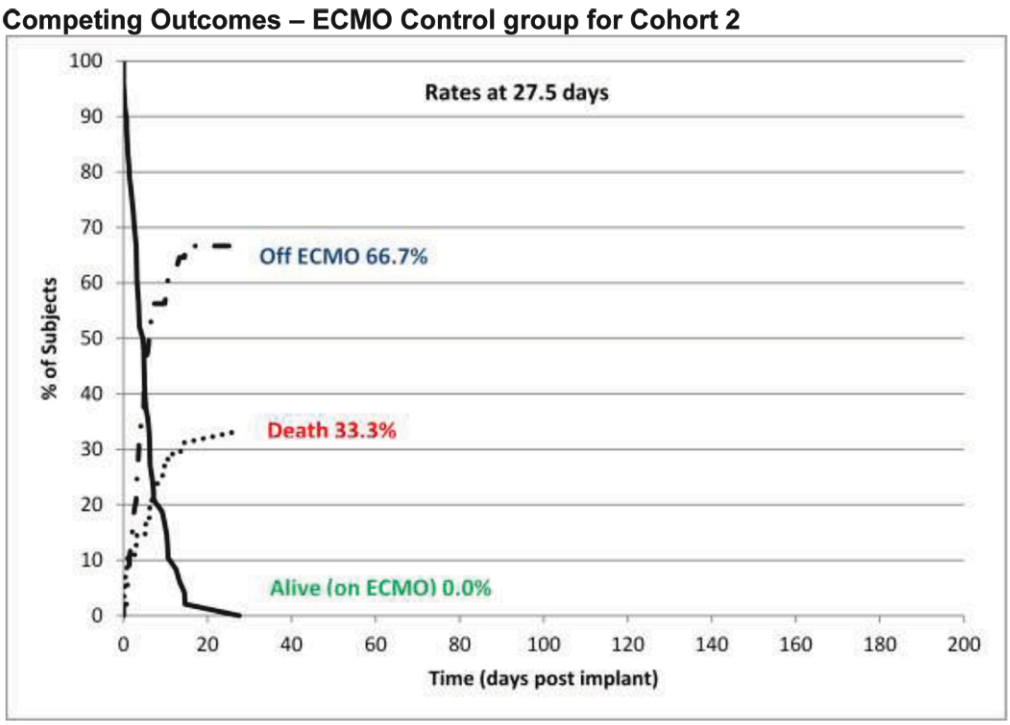


Fig. 3-7 Cohort 2 Control Group Competing Outcomes

a) Secondary Efficacy Results

There were two secondary efficacy objectives of the study. The first was to summarize the days of transplant eligible support.

Only one subject was removed from the transplantation listing at any point during their support. The subject (in Cohort 2) was first listed on day 3 of support (10/03/09) and then was delisted from 01/15/10 to 02/22/10 due to a neurological event. The subject was successfully transplanted on 04/10/10. The summary statistics of time of eligible support are detailed in the following table.

Days of Transplant Eligible Support

Cohort	N	Median	Mean ± Std	Range
Cohort 1	24	27.5	58.8 ± 56.1	0 – 174
Cohort 2	24	42.5	55.6 ± 44.3	3 – 151

Tab. 3-9 Days of transplant eligible support

The second objective was to show the ability to de-intensify concomitant hemodynamic support. At each visit, the subject's status was recorded with the following choices: sedated, intubated, on ECMO, awake, ambulating or eating. The following table summarizes those choices pre-implant, and at 2 weeks and 1 month post-implant. A subject could have more than one status subcategory checked.

Prior to implant, 22 of the 24 Cohort 1 subjects (92%) and 16 of 24 Cohort 2 subjects (67%) were sedated and/or intubated and over 30% were supported by ECMO immediately prior to device implant.

In Cohort 1 there were 7 subjects (7/20=35%) who were sedated and intubated at 2 weeks with 1 sedated and awake (1/20=5%). The other 12 (12/20=60%) were awake with some of those also ambulating and eating.

In Cohort 2, 6 subjects (6/20=30%) were still sedated and intubated at 2 weeks with 1 awake and intubated (1/20=5%) and the remaining 13 awake (13/20=65%). At 1 month post, those numbers drop to only 3 of the Cohort 1 and 4 of the Cohort 2 subjects remaining sedated and intubated.

Support Status at each Follow-up Visit

Time Point	Status (more than 1 could be checked)	Cohort 1 n=24	Cohort 2 n=24
Pre-implant N=24 In each cohort	Sedated	21 (87.5%)	16 (66.7%)
	Intubated	21 (87.5%)	14 (58.3%)
	On ECMO/other	8 (33.3%)	9 (37.5%)
	Awake	3 (12.5%)	12 (50.0%)
	Ambulating	0 (0.0%)	5 (20.8%)
	Eating	0 (0.0%)	8 (33.3%)
2 Weeks N=20 In each cohort	Sedated	8 (40.0%)	6 (30.0%)
	Intubated	7 (35.0%)	6 (30.0%)
	Awake	13 (65.0%)	14 (70.0%)
	Ambulating	3 (15.0%)	4 (20.0%)
	Eating	6 (30.0%)	12 (60.0%)
1 Month N=12 Cohort 1 N=17 Cohort 2	Sedated	4 (33.3%)	5 (29.4%)
	Intubated	3 (25.0%)	5 (29.4%)
	Awake	9 (75.0%)	13 (76.5%)
	Ambulating	3 (25.0%)	8 (47.1%)
	Eating	4 (33.3%)	9 (52.9%)

Tab. 3-10 Support status at each follow-up visit

3.6.6.2 Primary Safety

The total time on device of the Cohort 1 subjects was 1411 days. There were 96 serious adverse events (SAEs) for this cohort yielding a rate of **0.068 events per patient-day**. The 95% Poisson confidence interval was calculated as: [0.055, 0.083]. The total time on device for Cohort 2 was 1376 days. There were 109 SAEs for this cohort yielding a rate of **0.079 events per patient-day** with the confidence interval as [0.065, 0.096]. A summary of SAEs rates for each cohort is included in the first table of this clinical study section.

a) Infection Serious Adverse Events

Major Infection events were reported according to the Investigational Plan definition (which is the same as the INTERMACS definition). Any time an additional medication was added for treating a different organism a new SAE was reported (or adjudicated

as an event). The study design was intentionally broad with regard to setting a low threshold for calling an event an infection. Fever was defined at 38 degrees, WBC > 15,000, positive cultures from any source, or decision to start antibiotics with or without positive cultures were listed as an SAE and subsequently adjudicated. Each infection was counted as a separate event even when occurring concurrently in one patient, ensuring that the infection rate would not be under-reported.

In Cohort 1, 15 subjects had 35 total infectious events reported. In Cohort 1, a majority of subjects had pre-existing risks for infection including ventilation (83%), pre-implant ECMO support (33%), and previous cardiac surgery (21%).

In the larger subjects (Cohorts 2) there were fewer events (12 subjects with 24 events) which is as expected based on age and body size.

Outcomes of any of the subjects did not appear to be affected by infections as the deaths that occurred were not solely related to infection, even when one was present. These cases tended to have multi-factorial contributors such as stroke, end-organ failure, arrhythmias, or thromboembolism. All other subjects with a noted infectious SAE were transplanted or weaned. Infection had little impact on the transplant wait time since 99.3% of the total time the subjects were on support was considered transplant eligible time.

b) Major Bleeding Serious Adverse Events

Major Bleeding was the third most frequently reported SAE in Cohort 1 (10 subjects with at least one event). All bleeding events for Cohort 1 occurred in subjects less than 2 years old. Five of the 10 subjects in Cohort 1 with bleeding events were younger than 9 months old. Young infants have some degree of ineffective erythropoiesis. Hemoglobin subsequently falls to a nadir at around 2–3 months of age due to decreased RBC production. Anemia in acute or critical illness may be exacerbated by numerous factors including blood loss (due to hemorrhage or sampling), reduced RBC production (due to nutritional deficits, inflammatory processes or low erythropoietin levels) and increased RBC turnover due to hemolysis.

Cohort 1 subjects had a pre-implant history of transfusion in 92% (22/24), history of ECMO or previous VAD in 33% (8/24), and 21% (5/24) of subjects had previous cardiac surgeries. These factors along with the strict Major Bleeding definition could have contributed to the percentage of events reported.

Major Bleeding was one of most prevalent events in Cohort 2 with 12 of 24 (50%) subjects experiencing a bleeding event.

c) Hypertension Serious Adverse Events

Hypertension was reported per the protocol definition (consistent with the INTERMACS definition). An event was logged each time a subject's blood pressure reached the 95th percentile for age and was treated with an IV agent. Several hypertension events were reported in the early post-op periods. However, 75% (15/20) of the hypertension events were in Cohort 1 and 2 subjects who only received LVAD support. This is not surprising as it is common for patients supported only with left sided devices to require pharmacological support in order to optimize right ventricular function with agents that can cause hypertension, resulting in the concomitant need for agents to lower the blood pressure in the early post-operative period. Additionally, hypertension is one of the leading post operative cardiac surgical events for children, especially the younger children, possibly due to their reactive vasculature. In order to follow the event definition, hypertension events were reported when the values met the definition even if the subject was also on a pressor or in a period where the site was trying to optimize the overall hemodynamic status of the

subject in the early post-op period. There did not appear to be a correlation between Hypertension and Major Bleeding.

d) Neurological Dysfunction Serious Adverse Events

Four of the 48 (8.3%) Cohort 1 and 2 subjects experienced a neurological dysfunction with long term severe results (PSOM scores ≥2) and another 2 (4.2%) were withdrawn from support due to the neurological injury.

In Cohort 1, 7 of the 24 subjects experienced a neurological event. One subject experienced 2 ischemic events. Of the 7 subjects, 1 was withdrawn from support as a result of the neurological injury. Of the remaining 6 subjects, PSOM exams were performed post explant and 1 had no deficit (assessed 17 days post explant); 2 had mild deficits (23 and 221 days post explant), 1 had moderate deficit (82 days post) and 2 had severe deficits (PSOM score of 3 at 34 days post and score 4 at 54 days post).

In Cohort 2, 7 of the 24 subjects experienced a neurological event. Two of those subjects experienced both an ischemic and hemorrhagic event. Of the 7 subjects, 1 was withdrawn from support as a result of the neurological injury. Of the remaining 6 subjects, PSOM exams were performed post explant and 1 had no deficit (50 days post explant); 2 had mild deficits (27 and 49 days post explant), 1 had moderate deficit (357 days post) and 2 had severe deficits (PSOM scores of 10 at 29 and 38 days post).

This table summarizes the status information.

Summary of Neurological Event Status

Long term Result	Cohort 1 N=24	Cohort 2 N=24	Total N=48
No Deficit (PSOM 0.0)	1 (4.2%)	1 (4.2%)	2 (4.2%)
Mild (PSOM 0.5-1.0)	2 (8.3%)	2 (8.3%)	4 (8.3%)
Moderate (PSOM 1.5-2.0)	1 (4.2%)	1 (4.2%)	2 (4.2%)
Severe (PSOM ≥ 2.5)	2 (8.3%)	2 (8.3%)	4 (8.3%)
Support withdrawn	1 (4.2%)	1 (4.2%)	2 (4.2%)
TOTAL	**7 (29.2%)**	**7 (29.2%)**	**14 (29.2%)**

Tab. 3-11 Summary of neurological event status

Pump Replacement Due to Thrombus

During the course of the support, a clinician may have identified that a pump required replacement due to visualized thrombus within the blood pump. These replacements were not considered adverse events. However, these were nonetheless regarded as sentinel events due to their frequency and association with thromboemboli.

In the primary cohorts, 24 (50%) of the subjects had at least one pump replacement due to suspected thrombus (11 Cohort 1, 13 Cohort 2). The number of pump replacements ranged from 0 to 4 per subject. The average number of replacements per subject was 0.9 ± 1.2. However, subjects were supported on the device for varying lengths of time therefore it may be more informative to consider the replacements per length of time on device. The average replacements-per-day on device was 0.02 ± 0.03 per day.

At the IDE sites, 57 (52.3%) of the 109 subjects had at least one pump replacement due to thrombus (11 Cohort 1, 14 Cohort 1 CAP, 13 Cohort 2, and 19 Cohort 3). The number of pump replacements ranged from 0 to 6 per subject. The average number of replacements per subject was 1.1 ± 1.4 and the average replacements-per-day on device was 0.02 ± 0.03 per day.

Additionally, 95 subjects were enrolled at non-IDE sites. Of the 204 subjects, 93 (45.6%) subjects had at least one pump replacement due to thrombus (11 Cohort 1, 14 Cohort 1 CAP, 13 Cohort 2, and 19 Cohort 3, 36 Cohort 3 Non-IDE). The number of pump replacements ranged from 0 to 6 per subject. The average number of replacements per subject was 1.1 ± 1.4 and the average replacements-per-day on device was 0.02 ± 0.03 per day.

Cohort	N	# Subjects with at least 1 replacement	Total number of replacement	Replacements per Subject	Total Days on Device	Replacements per Days on Support	Time to first replacement (days)
primary Cohorts*	48	25 (50.0%)	43	0.9 ± 1.2 0 - 4	2787	0.02 ± 0.03 0.00 - 0.13	24.1 ± 19.7 4 - 105
IDE Cohorts	109	57 (52.3%)	114	1.1 ± 1.4 0 - 6	6350	0.02 ± 0.03 0.00 - 0.18	19.1 ± 16.9 2 - 105
Non-IDE Cohorts	95	36 (37.9%)	58	0.6 ± 1.0 0 - 4	7240	0.01 ± 0.03 0.00 - 0.27	41.9 ± 44.6 2 - 198
Total	204	93 (45.6%)	172	0.8 ± 1.2 0 - 6	13590	0.02 ± 0.03 0.00 - 0.27	27.8 ± 32.3 2 - 198

Tab. 3-12 Pump replacement

* Note: the 48 subjects in the “Primary Cohorts” group are a subset of the “IDE Cohorts” group (n=109)

3.6.6.3 Death information

Two subjects in each of the primary cohorts died after support was withdrawn. The 4 subjects were supported a median time of 28.5 days ranging from 0 to 144 days (mean ± std: 50.3 ± 64.4 days). Of the 4 subjects who died, 75% (3/4) were supported with ECMO at the time of EXCOR implant.

The CEC reviewed all deaths at the IDE sites and assigned primary and secondary causes of death. These causes are summarized by subject in the following table.

Patient	Days on Device	Primary Cause	Secondary Cause(s)
COHORT 1 (2 deaths/ 24 subjects)			
#1	0	Pulmonary Respiratory Failure	Cardiovascular: Left A-V valve regurgitation
#2	38	CNS: Multiple ischemic strokes	None
COHORT 2 (2 deaths/ 24 subjects)			
#3	144	Other: Arterial CNS and non-CNS Thromboembolism	Infection
#4	19	CNS: Large ischemic strokes with hemorrhagic conversion	Other: Tonsillar herniation

Tab. 3-13 Primary and secondary cause of death

3.6.7 Conclusion

Despite the reported SAEs, 42 of the 48 subjects supported by the EXCOR were adequately supported to transplant and 1 subject was able to be weaned successfully from the device after 9 days of support yielding an 89.6% success rate (43/48). The device supported children safely to cardiac transplantation for a median transplant eligible time of 27.5 and 42.5 days for cohort 1 and 2 respectively. Only one subject was temporarily removed from transplant eligibility during their support and was eventually relisted and transplanted.

Data that strongly supports the consideration for probable benefit is summarized for both Cohort 1 and 2 subjects as shown in the following tables.

Probable Benefit

Cohort	N	Outcome				Success (Transplant or Weaned-Recovered)
		Transplant	Weaned-Recovered	Weaned-Failure	Died	
Cohort 1	24	21	0	1	2	21/24 (87.5%)
Cohort 2	24	21	1	0	2	22/24 (91.7%)
Total	**48**	**42**	**1**	**1**	**4**	**43/48 (89.6%)**

Tab. 3-14 Probable Benefit

Post-Explant/Transplant Follow-up

Cohort		Outcome	30 days post-explant		1 year post-explant	
	N	# Explanted	# (%) alive 30 days	Lost to Follow-up	# (%) alive 1 Year	Lost to Follow-up
Cohort 1	24	22	22/22 (100%)	n/a	17/22 (77%)	0
Cohort 2	24	22	21/22 (95%)	1*	16/17 (94%)**	1
Total	**48**	**44**	**43/44 (97.7%)**	**1**	**33/39 (85%)**	**1**

* 1 subject was weaned and returned to home

** 5 subjects have regular contact with the site for post transplant care but are not 1 year post-explant as of this report: 3 subjects are due in June (last report alive at 313, 257 and 250 days), 1 subject is due in July (last report alive at 170 days) – verbal report; denominator includes 1 LTF

Tab. 3-15 Post-explant/transplant status follow up

Beyond the primary endpoint of survival to transplant, the majority of subjects remain alive at 1 year post-explant/transplant as noted in the previous table.

HDE regulations require the device under study to show **reasonable safety and probable benefit**. In the EXCOR® Pediatric IDE trial the device demonstrated probable benefit as a bridge to transplantation in patients who are transplant eligible with severe left ventricular or biventricular dysfunction. The majority of patients implanted with the EXCOR were transplant eligible during device support with adequate end organ function and decreasing need for hemodynamic support such as intubation, sedation or ECMO support. While the concomitant support decreased, the subjects were able to spend more time awake, eating and ambulating.

The benefits offered to subjects implanted with the EXCOR® Pediatric include additional time to await transplant and improved hemodynamics allowing removal of pre-implant hemodynamic support allowing for increase time awake, ambulating and eating contributing to post implant transplant eligible wait times. These far-reaching benefits outweigh the risks associated with the adverse events that occurred.

3.7 Post Approval Study Summary

3.7.1 Study Objective

The purpose of the Post Approval Study (PAS) of the EXCOR® Pediatric VAD was to evaluate whether safety and outcomes of the device use in the commercial setting were comparable to the safety and outcomes of the device use in the IDE study.

3.7.2 Study Design

The study was an “all-comers” prospective study maintained by Berlin Heart consisting of pediatric patients aged 0-21 years implanted according to the IFU with the EXCOR® Pediatric who were transplant eligible children in need of mechanical circulatory support and who consented to be enrolled into the study.

3.7.3 Study Population

The study included subjects who met the Inclusion and Exclusion Criteria included below and for whom the EXCOR® Pediatric was indicated and not contraindicated per the product labeling.

Inclusion Criteria

- Patient requires mechanical circulatory support and is eligible for cardiac transplantation
- Legal guardian and patient (if age appropriate) understands the nature of the implant procedure and are willing to comply with associated follow-up evaluations, and provide written informed consent and assent prior to the procedure

Exclusion Criteria

- Patient is currently enrolled in EXCOR® Pediatric pre market study
- Patient is currently participating in another investigational device or drug trial which would confound the results of the study

3.7.4 Data source

Berlin Heart sponsored web-based Registry.

3.7.5 Key Study Endpoints

Primary Safety Objective / Endpoint

The primary safety objective of the study was to demonstrate that the serious adverse event (SAE) rate in subjects implanted with the EXCOR® Pediatric in this study was not greater than the rate experienced in the IDE study.

The primary endpoint was the SAE rate which was calculated as the total number of SAEs divided by the sum of days all subjects were supported on the EXCOR® Pediatric device.

A clinical events committee (CEC) met regularly during the course of the study to adjudicate the protocol-specified SAEs: major bleeding, major infection and neurological dysfunction events, and device malfunctions. The CEC also reviewed and assigned cause of death to any subject who died as a result of withdrawal of device support.

Primary Efficacy Objective / Endpoint

The primary effectiveness objective for the study was to assess the outcome following implantation of the EXCOR® Pediatric for transplant eligible children in need of mechanical circulatory support. The endpoint was defined as transplant, recovery of left ventricular function or death.

3.7.6 Total number of Enrolled Study Sites and Subjects, Follow-up Rate

A total of 39 subjects were enrolled at 19 investigational sites. All subjects were followed for the duration of device support. Subjects explanted from the device will continue to be followed for 24 months post explant.

3.7.7 Study visits and length of follow-up

Clinical data recorded in hospital records was collected at the time of pre-implant, implant, planned follow-ups (3 weeks, 6 weeks, 3 months, 6 months and every 3 months thereafter while on device support and up to transplant/recovery). Following explant of the device, follow-up visits were scheduled at hospital discharge, 12 months post explant and 24 months post explant.

3.7.8 Results

3.7.8.1 Primary Safety

The total time on device support for the study subjects was 4216 days. There were 102 SAEs reported for the 39 subjects yielding a rate of 0.024 events per patient-day (95% Poisson confidence interval: 0.020 – 0.029). The difference between the event rate in the PAS study and the IDE rate 0.071 was statistically significantly lower (p-value <0.0001).

The following table summarizes the reported SAEs with their adjudicated results.

Event Category	**# event**	**# subjects with event** n (% of 39)	**Events / Subject** # /39
Adjudicated SAEs			
Major Bleeding	23	16 (41.0%)	0.59
Major Infection:	20	15 (38.5%)	0.51
Localized non-device	3	3 (7.7%)	0.08
Percutaneous Site and/or Pocket Infection	8	6 (15.4%)	0.21
Internal Pump Component, Inflow or Outflow Tract Infection	2	2 (5.1%)	0.05
Sepsis	7	7 (17.9%)	0.18
Neurological dysfunction:	17	13 (33.3%)	0.44
TIA	0	0 (0.0%)	0.00
Ischemic CVA	8	6 (15.4%)	0.21
Hemorrhagic CVA	5	5 (12.8%)	0.13
Ischemic/Hemorrhagic CVA	4	3 (7.7%)	0.10
New abnormality of head ultrasound	0	0 (0.0%)	0.00
EEG positive for seizure activity with or without clinical seizure	0	0 (0.0%)	0.00
Other			
• Covert stroke	3	3 (7.7%)	0.08
• Seizure	2	2 (5.1%)	0.05
• Encephalopathy	1	1 (2.6%)	0.03

Tab. 3-16 EXCOR® Pediatric Post Approval Study Serious Adverse Events

Event Category	# event	# subjects with event n (% of 39)	Events / Subject # /39
Other SAEs			
Hepatic Dysfunction	2	2 (5.1%)	0.05
Hypertension	4	4 (10.3%)	0.10
Pericardial effusion with tamponade	1	1 (2.6%)	0.03
Pericardial effusion without tamponade	3	3 (7.7%)	0.08
Psychiatric episode	1	1 (2.6%)	0.03
Renal Dysfunction-Chronic	1	1 (2.6%)	0.03
Respiratory failure	9	7 (17.9%)	0.23
Right heart failure	3	3 (7.7%)	0.08
Venous Thromboembolism	3	2 (5.1%)	0.08
Other	9	8 (20.5%)	0.23
TOTAL	102	32 (82.0%)	2.36

Tab. 3-16 EXCOR® Pediatric Post Approval Study Serious Adverse Events

3.7.8.2 Primary Efficacy Endpoints

Twenty-seven (27) of the 39 (69.2%) subjects were successfully transplanted or weaned from the device. Total support time ranged from 0 to 457 days with an average time of 108.1 days (standard deviation=118.9) and median of 63 days (IQR=20, 160).

The following table details the outcomes for the study subjects.

Outcome	n (% of 39)
Transplant	25 (64.1%)
Weaned; alive > 30 days	2 (5.1%)
Escalated to ECMO [1]	2 (5.1%)
Death	10 (25.6%)

[1] subjects died after transition

Tab. 3-17 EXCOR® Pediatric Post Approval Study Outcomes

3.7.8.3 Study Strength and Weaknesses

Strengths:

The study was a prospective study with pre-defined hypotheses and statistically calculated sample size. A central committee adjudicated the major serious adverse events (major bleeding, major infection, neurological dysfunction) as well as device malfunctions and deaths. Follow-up rate was 100% as all subjects remained in the hospital while on device support and, therefore, all follow-up visits were conducted.

Weaknesses:

The enrolled subjects showed a higher risk profile when compared to the IDE cohort and were smaller, younger, spent longer time on support, and more patients presented with CHD, especially single ventricle physiology.

4 Description: blood pump, cannulae and accessories

EXCOR is an extracorporeal electro-pneumatically driven ventricular assist device. It can be used for either univentricular or biventricular support. EXCOR is comprised of the following permanently active components:

- extracorporeal blood pump(s)
- inflow and outflow cannula(e)
- 1 driving tube for each blood pump
- Ikus

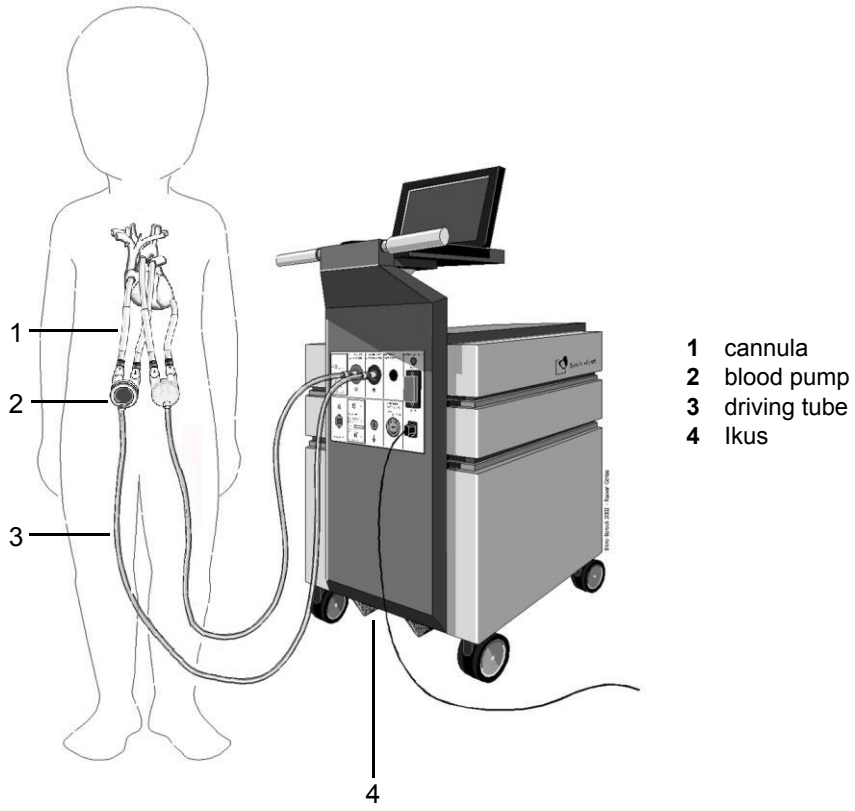
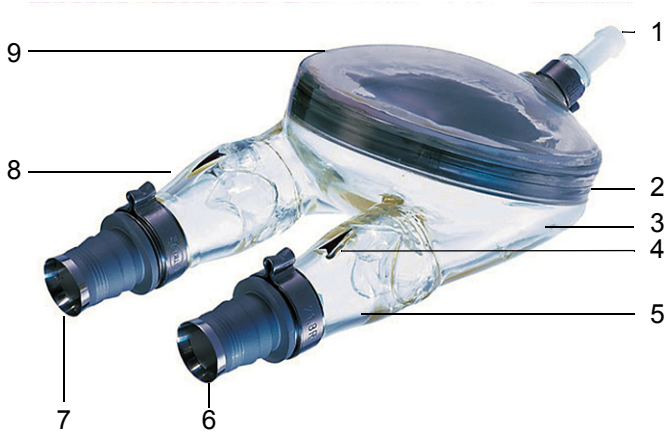


Fig. 4-1 EXCOR shown in situ as a biventricular assist device in pediatric application

Overview

The blood flows from the atrium or the ventricle through the inflow cannula into the blood chamber of the pump and then from this blood chamber through the outflow cannula into the aorta or into the pulmonary artery. A driving tube is used to connect the air chamber of the pump to the electro-pneumatic Stationary Driving Unit Ikus. Ikus generates the suction and driving pressures required to move the triple-layer membrane separating the blood chamber from the air chamber.

4.1 EXCOR blood pumps



1 driving tube connector
2 triple-layer membrane
3 blood chamber (de-airing nipple at back of pump)
4 arrow mark: indicates blood flow direction
5 inflow stub
6 titanium connector: inflow stub – inflow cannula
7 titanium connector: outflow stub – outflow cannula
8 outflow stub
9 air chamber

Fig. 4-2 60 ml blood pump

EXCOR blood pumps have a transparent polyurethane (PU) housing which is divided into an air chamber and a blood chamber by a triple-layer membrane.

The blood chamber has an inflow and an outflow stub to which the inflow and outflow cannula, respectively, are connected. The pump stubs themselves are made of polyurethane, the end of each stub is fitted with a titanium connector to which the cannula will be connected. The valves located in the pump stubs keep the blood flowing in one direction. EXCOR blood pumps are available with three-leaflet valves made of polyurethane (10 - 60 ml stroke volume).

All surfaces of the pump coming into contact with the blood are coated with a Carmeda® BioActive Surface (CBAS) coating. The transparent casing of the blood pump allows easy visual monitoring of the filling and emptying of the blood chamber.

The blood pump is equipped with a de-airing nipple which is used for de-airing the blood chamber when the pump is being commissioned.

The air chamber of the pump is equipped with a driving tube connector. This connector is used to connect the blood pump to the driving tube through which air is pumped from the Ikus. Ikus generates the suction and driving pressures required to move the blood pump's triple-layer membrane. A graphite powder layer is located between the membrane layers in order to minimize friction.

4.2 EXCOR cannulae

3 different types of cannulae are available for EXCOR in various sizes for each type:

- atrial cannulae (as inflow cannulae)
- LV apex cannulae (as inflow cannulae)
- arterial cannulae (as outflow cannulae)

The cannulae are made of tissue-friendly silicone. Polyester-velour suture rings enable convenient and safe anastomosis of the cannulae. The mid section of all cannulae is covered with polyester-velour in order to promote good ingrowth of the cannulae where they pass through the skin.

Some arterial cannulae have a shaping wire which allows the cannulae to be adapted to each individual patient's anatomic conditions.

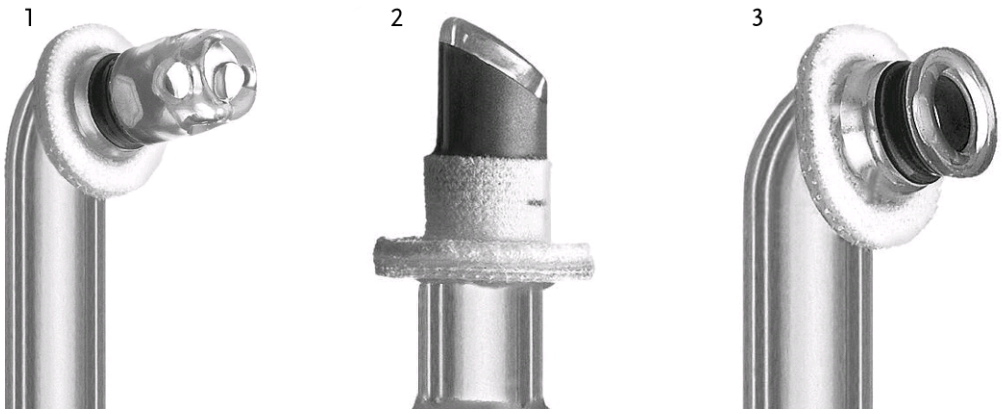


Fig. 4-3 Cannula heads: 1) atrial cannula, 2) LV apex cannula, 3) arterial cannula

4.3 EXCOR accessories

The following EXCOR accessories are required in order to commission and operate EXCOR:

- 1 driving tube (PVC) for each blood pump
- 2 tank units
- 1 accessory (T00L-002) set which includes:
  - membrane set
  - de-airing set (2 x trocar, 2 x de-airing tube)
  - de-airing hammer
  - tube connecting set (cable ties, cable-tie gun)

There is enough material in 1 accessory set (T00L-002) to commission 2 EXCOR blood pumps.

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5 Implantation: Preparations in the operating room

NOTE: This chapter omits safety instructions, infomation and procedures that refer to the Ikus exclusively. Please refer also to the IFU.

5.1 Preparing the components and materials required

NOTICE

Selection of blood pump(s): see section section 12.1: Overview: Product range and possible combinations, page 129.

ADVICE

It is advantageous to provide a sterile table on which to place the prepared sterile components.

General (all sterile)

- 500 ml sterile injectable saline
- 2 small sterile basins
- 50 ml disposable syringe with luer lock connector
- suture (to secure the trocar to the de-airing nipple and the de-airing tube to the trocar)
- heavy scissors
- towel clamp, tube clamp
- other instruments and equipment as required for open-heart surgery

EXCOR components and accessories

- blood pump(s), each with a pump seal
- 1 driving tube for each blood pump
  - univentricular: driving tube, red
  - biventricular: 1 red driving tube and 1 blue driving tube
- inflow cannula(e) (atrial or LV apex cannula)
- outflow cannula(e)
- accessory set (T00L-002) for blood pumps with PU valves
  - membrane set
  - de-airing set (2 x trocar, 2 x de-airing tube)
  - de-airing hammer
  - tube connecting set (cable ties, cable-tie gun)

5.2 Checking and adjusting the settings of the cable tie gun

Before using the cable tie gun contained in the EXCOR *Tube connecting set* the accuracy of settings has to be checked and if necessary to be corrected.

Fig. 5-1 Cable tie gun

INSTRUCTION

1. Check if the following values are set:
   - coarse adjustment on STD (*2*)
   - fine adjustment on 5 (*1*)

Fig. 5-2 Checking the adjustment

2. In the case of deviations loosen the screw (*4*) and disassemble the locking cap (*3*).

Fig. 5-3 Disassemble the locking cap

3. Adjust the above-mentioned values with the adjusting wheels (*6* and *5*). Begin with adjusting wheel *6*.

Fig. 5-4 Adjusting the settings

4. Assemble the locking cap (*3*) and secure it with the screw (*4*).

Fig. 5-5 Assemble the locking cap

5.3 Unpacking the sterile components

WARNING

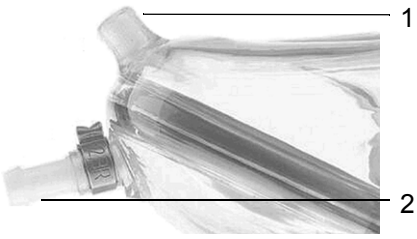
Only use sterile components which have been delivered in undamaged sterile condition (sterile packaging intact, expiration date not expired).

Only use blood pumps which have an undamaged aluminum-coated outer packaging.

INSTRUCTION

1. Pump: a non-sterile person opens the aluminum-coated package and removes the pump in its double sterile packaging.
2. The non-sterile person opens the outer sterile package.
3. A sterile person takes out the inner sterile package, opens it and places the components on the prepared sterile field.

5.4 Moving the membrane to the end-of-diastole position



1 de-airing nipple (blood chamber)
2 driving tube connector (air chamber)

Fig. 5-6 De-airing nipple and driving tube connector

INSTRUCTION

1. Pick up adapter tube, disposable syringe (membrane set) and the pump.
2. Connect the adapter tube to the disposable syringe.
3. Connect the free end of the adapter tube to the driving tube connector of the blood pump.
4. Remove all air from the air chamber of the pump. The blood pump membrane is now in the end-of-diastole position.
5. Seal the adapter tube with a tube clamp in order to keep the membrane in this position.

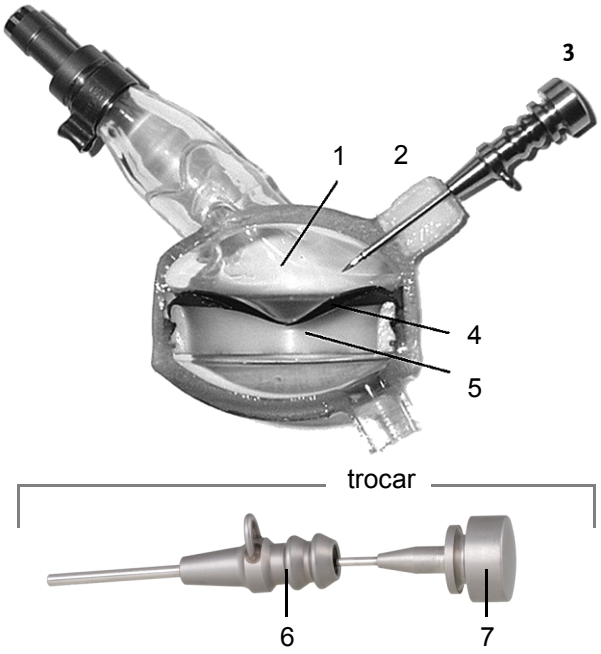
5.5 De-airing the blood pump

WARNING

Make sure that no particles or liquids enter the air chamber of the blood pump. Otherwise, the membrane may be damaged and the patient may not receive adequate support.

Prepare and place the following ready for use:

- blood pump(s) with pump seal(s)
- 1 de-airing set (trocar and a de-airing tube) for each blood pump
- 50 ml disposable syringe for each blood pump



1 blood chamber
2 de-airing nipple
3 trocar (de-airing needle with obturator in place)
4 membrane in end-of-diastole position
5 air chamber
6 de-airing needle
7 obturator

Fig. 5-7 Pump with trocar in place (de-airing needle with inserted obturator)

5.5.1 Inserting the de-airing needle

WARNING

The membrane must be kept in the end-of-diastole position. Keep the clamped membrane set connected to the blood pump.

INSTRUCTION

1. Take hold of the trocar (de-airing needle with obturator) and remove the protective silicone cap.
2. Push the trocar as pictured above as far as it will go through the center of the blood pump's de-airing nipple. Never turn the trocar when inserting it, this increases the risk of removing a large piece of the silicone material in the de-airing nipple.
3. Remove the obturator.
4. Withdraw the de-airing needle by approx. 2 mm. IMPORTANT: The tip of the cannula should still be visible in the blood chamber.
5. Use the suture to fix the de-airing needle to the de-airing nipple.
6. Remove the adapter tube from the pump.

5.5.2 Rinsing and filling the blood pump

ADVICE

Before commencing surgery, mark the points for the exit sites of the cannulae. The aim is to achieve a stable final position of the cannulae without exerting any tension on the skin. Caution: with biventricular support, 2 of the 4 cannulae will cross each other. This crossing point should be outside of the thorax as far as possible.

Fill and empty the pump once or twice with sterile injectable saline:

INSTRUCTION

1. Push the free end of the de-airing tube onto the trocar as far as it will go. Secure the de-airing tube to the trocar with a suture tie.
2. Fill the syringe with sterile injectable saline.
3. Connect the syringe to the stopcock end of the de-airing tube.
4. Slowly fill the pump with sterile injectable saline. Rock the pump back and forth to move any bubbles to the outflow stub.
5. Close the stopcock on the de-airing tube.
6. Tap the blood pump body gently in order to free all remaining bubbles. Remove all air from the pump through the outflow connector.
7. Use the seal caps to close the titanium cannula connectors.
8. Place the pump ready for connection with the connectors pointing up.

6 Implantation - surgical procedure

This chapter describes the product-specific measures to be observed when implanting an EXCOR blood pump.

NOTE: This chapter omits safety instructions, information and procedures that refer to the Ikus exclusively. Please refer also to the IFU.

Unless any specific instructions to the contrary are given, the same protocol as for any other major cardiothoracic surgical procedure should be followed. Implantation is accomplished using a CPB with bicaval cannulation. Implantation can be achieved with induced ventricular fibrillation or on a beating heart, hypothermia is usually not required.

WARNING

After implantation each cannulae and all connections must be inspected for it's solidity, safeness and tightness.

Do not start pump operation until the blood pump is completely free of air!

Do not touch or manipulate the blood pump with pointed or sharp-edged objects (e. g. surgical instruments)!

Do not touch or manipulate the drive lines with pointed or sharp-edged objects (surgical instruments, wire brushes, etc.), otherwise these components could be damaged.

If a cannula is bent with flexible metal reinforcement to adjust it to the anatomical conditions: determine by visual inspection that the blood flow in the cannula is not restricted.

When positioning the driving tubes mitigate the risk of adverse tubing and line incidents by routing the driving tubes in a clear pattern toward the feet and to the side.

When using blood pumps of equal size on the left and right, verify that the pulmonary circulation is not being overloaded. Otherwise, pulmonary edema may result.

NOTICE

For the suture use an appropriate suture material. It should be a nonabsorbable monofilament, not traumatizing material.

ADVICE

For BVAD, carry out anastomosis of the cannulae in the following order:
apical cannulation:
1. LV apex
2. right atrium
3. pulmonary artery
4. aorta

atrial cannulation:
1. left atrium
2. right atrium
3. pulmonary artery
4. aorta

6.1 Cannula exit sites

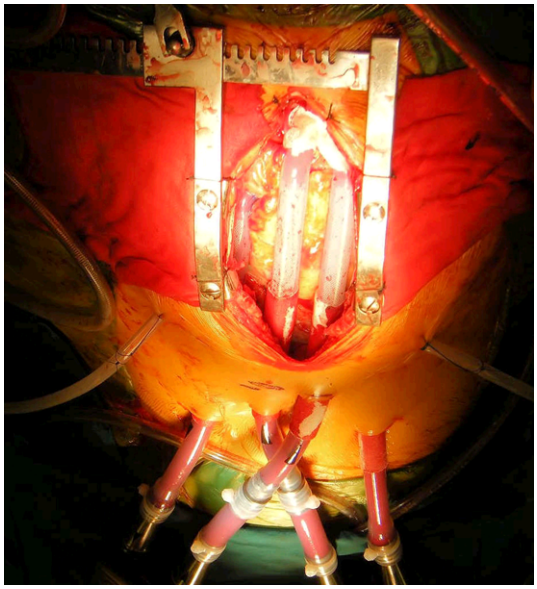
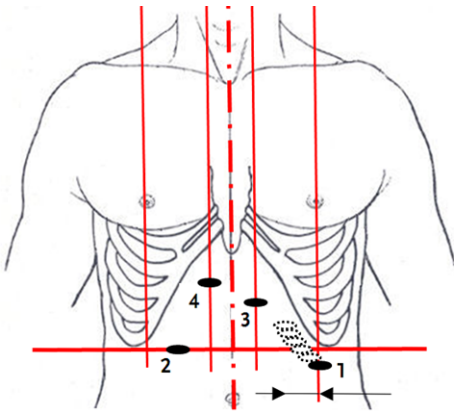


Fig. 6-1 Cannula position following implantation



1 Aortic cannula
2 PA cannula
3 RA cannula
4 LV apex cannula

Possible exit site for LV apex cannulation (depending on the size of the patient's heart)

Fig. 6-2 Suggested cannulae exit sites (Example: BVAD with LV apex cannulation)

6.2 Use of the cannula tunneling tip

The cannula tunneling tip is a sterile disposable product and is supplied with each cannula. Sizes available: see Fig. 6-3, page 57. Staged cannulae are supplied with 2 different tunneling tips.

INSTRUCTION

1. Push the cannula tunneling tip firmly into the distal end of the cannula.
2. Advance the forceps through the subcostal incision and the cannula tunnel into the mediastinum, so that the cannula tunneling tip can be gripped.
3. Use the forceps to firmly grip the flat end piece, pull it through the cannula tunnel and the skin incision and position it.
4. Carefully remove the tunneling tip from the cannula by bending it back and forth.

Refer to the respective cannula type as described in sections section 6.3: Cannulae, cannula extension set and connecting set, page 57 to section 6.7: Arterial cannula(e), page 65 of the instruction for use to determine the sequence of cannulae anastomosis and tunneling.

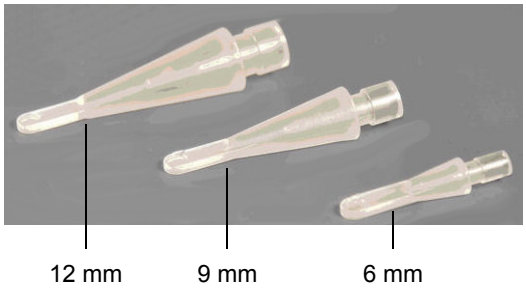
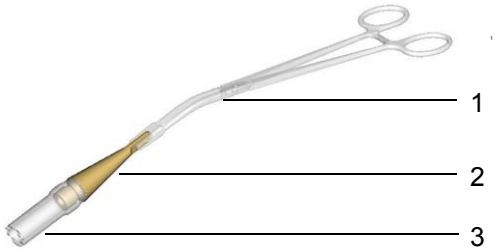


Fig. 6-3 Available sizes of cannula tunneling tips



1 Dressing forceps
2 Cannula tunnelling tip
3 Cannula

Fig. 6-4 Use of cannula tunneling tip

6.3 Cannulae, cannula extension set and connecting set

To avoid damages of cannulae careful attention should be paid to the following safety precautions.

The use of the cannula extension set / of the connecting set involves further safety precautions. See section 6.3.2: Instructions for Use: Cannula extension set and connecting set, page 59.

WARNING

The Cannula Tunneling Tip (provided with each cannula) should be used during implantation of the EXCOR system.

If it is necessary to apply a clamp directly to the cannula in order to pull the cannula through the skin, the following procedures should be observed:
- Position the clamp at the distal end of the cannula
- After the cannula has been pulled through the skin, cut off and discard the part of the cannula where the clamp was applied.

If it is necessary to clamp any other part of the cannula (cannula extension set / connecting set resp.) that is not covered with velour, cover the part that will be clamped with a gauze sponge.

If replacement of an EXCOR blood pump is required, the following procedures should be observed:
- The cable tie covering the EXCOR cannula on the stub of the blood pump should be removed carefully. Use an appropriate blunt tool. IMPORTANT: never use a sharp instrument, for example, a scalpel or scissors, to remove the cable tie. This may cause damage to the cannula.
- If a cannula extension set/ connecting set needs to be cut for a pump replacement, ensure that there will be sufficient length of the tube part remaining to meet the minimum length recommendations. See Tab. 6-2, page 68.

Do not kink the drivelines. Otherwise there might not be sufficient pump output

Do not kink the cannulae needlessly. Otherwise there might not be sufficient pump output. Moreover, cannulae might be damaged.

At least daily, the EXCOR cannulae should be inspected for signs of wear or damage. ADVICE: To avoid needless kinking of the cannulae use a mirror for inspection of the bottom side of the blood pump.

In no case should the cannulae either be kinked directly at the connector to the blood pump or at the transition area between velour and silicone.

WARNING

6.3.1 Description: Cannula extension and connecting sets

Berlin Heart supplies connecting sets to bridge different connector diameters in the blood pump and cannula (6/9, 9/12). This allows for greater flexibility when combining blood pumps and cannulae. The connecting set may be used during implantation or during the further course of therapy.

Berlin Heart supplies cannula extension sets for blood pumps/cannula combinations with diameters of 6/6, 9/9 and 12/12.

The cannula extension set is used to lengthen the piece of cannula which remains after the cannula has been shortened.

These sets could be neccessary in the following contexts:

- during implantation
- when replacing a blood pump
- when cutting off a piece of cannula (due to visible deposits or damaged cannula)

The cannula extension / connecting sets thus guarantee that the blood pump and cannulae can still be safely connected with one another and that the cannulae and titanium connectors on the blood pump can still be visually inspected.

Each cannula extension / connecting set consists of two cannula extensions / connectors. Each cannula extension / connector comprises a double-sided titanium connector to which a piece of tube is connected on one side.

Fig. 6-5 Cannula extension: titanium connector with tube section

6.3.2 Instructions for Use: Cannula extension set and connecting set

Cannula extension set

WARNING

If, on *further shortening* of the cannula, visual inspection of the titanium connector on the blood pump is no longer possible: use the cannula extension set.

Cannula extension set and connecting set

WARNING

The cannula extension set and the connecting set should only be used if neccessary, since the basic risk of thrombogenesis and deposits increases each time the cannula is extended.

Do not combine the connecting set with stage cannulae in such a way that multiple diameters are bridged. Otherwise, the pump will not fill or empty completely.

Secure each of the connections with at least 1 cable tie. Otherwise, the connections may loosen over time and the cannula extension set / the connecting set may become separated from the blood pump.

All effort should be made to minimize the manipulation and distortion of the blood pumps and cannula during the removal of the cable tie(s) to prevent mobilization of deposits.

If it is necessary to clamp any other part of the cannula (cannula extension set / conecting set resp.) that is not covered with velour, cover the part that will be clamped with a gauze sponge

When using a cannula extension set / a connecting set it may be necessary to shorten the respective connecting tube, but the minimum length must be maintained. See Tab. 6-2, page 68.

Article	Diameter / Diameter reduction	Minimum length
Cannula extension set		
A06-006	6 mm	55 mm
A09-009	9 mm	60 mm
A12-012	12 mm	75 mm
Connecting set		
A06-009	9 to 6 mm	60 mm
A09-012	12 to 9 mm	75 mm

Tab. 6-1 Cannula extension set / connecting set: minimum length of tube section

Preparation

INSTRUCTION

1. Take hold of the cannula extension set (the connecting set resp.).
2. If necessary: cut the section of tube to the desired length. Cut perpendicular to the axis of the tube section and ensure a straight cut. Ensure that the required minimum length is maintained. See Tab. 6-2, page 68. Ensure that the end position of the tube sections, cannulae and blood pump are free of tension.
3. Make sure that the cannulae are free of deposits.

During implantation/ When replacing a blood pump

INSTRUCTION

1. Connect the cannula extensions (the connectors resp.) with the blood pump. To do so, push the section of the cannula extension (the connector resp.) onto the titanium connector of the blood pump. Prime the blood pump with the cannula extensions (with connectors resp.).
2. Connect the cannula extensions (the connectors resp.) with the cannulae. To do so, push each cannula onto the titanium connectors of the cannula extension (of the connectors resp.) while flushing with sterile injectable saline solution.
3. Proceed according to context. See section 5.4: Moving the membrane to the end-of-diastole position, page 52 and section 10.1: Replacing the blood pump(s), page 103.

Without replacing a blood pump

INSTRUCTION

1. Push the free end of the cannula onto the titanium connector of the cannula extension (of the connector resp.).
2. Flush the tube sections with sterile injectable saline solution.
3. Push the sections of tube, which are free of air, onto the titanium connectors of the blood pump.
4. Proceed according to context. Act according to 10.1.2, page 104 and 10.1.3, page 105 respectively but without replacing the blood pump.

Securing the connections

INSTRUCTION

1. Secure each connection between silicone tube and titanium connector with at least 1 cable tie. See section 6.12: Securing the connections, page 76.

6.4 Access

INSTRUCTION

1. Median sternotomy. Make sure that there is absolutely no bleeding.
2. Insert standard cardiopulmonary bypass cannulae (bicaval cannulation).
3. Initiate extracorporeal circulation.
4. Place a vent in the left atrium, if necessary.

6.5 LV apex cannula

Refer to section 6.2: Use of the cannula tunneling tip, page 57.

6.5.1 Anastomosis of inflow cannula with LV apex

WARNING

During anastomosis of the LV apex cannula, make sure that the cannula head is facing in the right direction: the long side of the head should be parallel to the lateral wall. This prevents the ventricular lateral wall from being sucked into the tip of the cannula. After the cannula head has been placed, its position can be checked by means of the flow direction arrow on the cannula body (except LV apex cannulae C10A-030, C14A-040, C18A-020). The arrow is aligned with the long side of the cannula head (see Fig. 6-7, page 62).

INSTRUCTION

1. If indicated, initiate ventricular fibrillation as needed.
2. Apical excision of the LV: The ideal implant position of the LV cannula is slightly off-center of the LV apex toward the lateral wall. The distance from LAD/ septum to the center of the excised muscle core is about 2 cm for children (see 1 in Fig. 6-7, page 62).

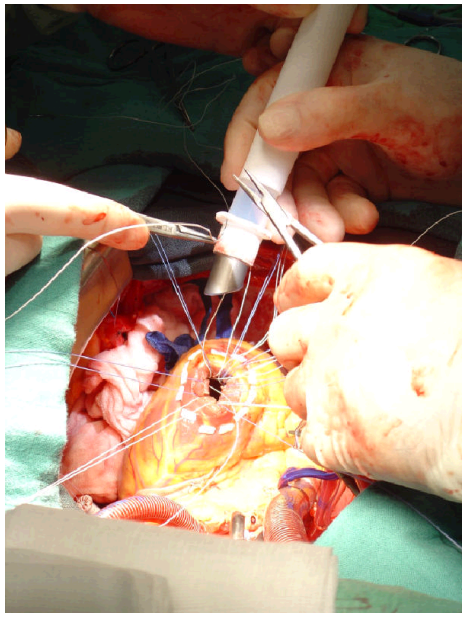


Fig. 6-6 Anastomosis of LV apex cannula

3. We recommend to excise a circular apical core with a diameter slightly smaller than the size of the cannula head.
4. Start with muscle core incision on the side away from the septum/ LAD (see 2 in Fig. 6-7, page 62) to avoid septal injury.
5. Check left ventricle for thrombi and excise the excess trabeculae.

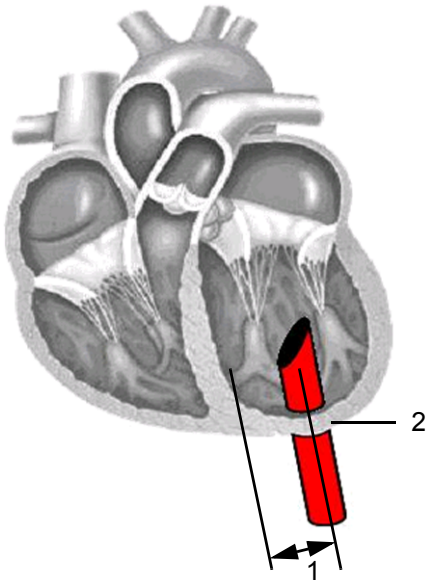


Fig. 6-7 Ideal position of the LV apex cannula

1 ca. 2 cm
2 see point 4 of instructions

Fig. 6-8 Head of LV apex cannula

1 Long side of LV apex cannula head

6.5.2 Creating a transcutaneous tunnel for the LV apex cannula

WARNING

Always use the cannula tunneling tip provided (see section 6.2: Use of the cannula tunneling tip, page 57) to advance the cannula through the prepared transcutaneous tunnel. Never use a sharp surgical instrument directly on the cannula.

Make sure that the blood pump and cannulae come to rest in a stable position without tension.

Do not touch or manipulate the silicone cannulae with pointed or sharp-edged objects (e. g. surgical instruments).

If it is necessary to apply a clamp directly to the cannula in order to pull the cannula through the skin, the following procedures should be observed:
- Position the clamp at the distal end of the cannula
- After the cannula has been pulled through the skin, cut off and discard the part of the cannula where the clamp was applied.
- If it is necessary to clamp any other part of the cannula that is not covered with velour, cover the part of the cannula that will be clamped with a gauze sponge.

The skin incision must be slightly smaller than the cannula diameter (to ensure good ingrowth) but large enough to prevent necrosis.

Plan the cannula exit sites appropriately. Leave an adequate bridge of skin and subcutaneous tissue between the cannula exit incisions to prevent breakdown and necrosis of the skin and tissue. If possible, the cannula exit sites should be on different planes (see Fig. 6-2, page 56).

INSTRUCTION

1. Prepare the transcutaneous tunnel. Ensure that the incision is large enough.
2. Incise the pericardium widely in a lateral direction. Prepare the cannula tunnel by blunt dissection. IMPORTANT: Do not tunnel transperitoneally.
3. Tunnel the LV apex cannula through the transcutaneous passage by using a pair of forceps to firmly grip the flat end piece of the tunneling tip and pull it through the cannula tunnel and the skin incision.
   IMPORTANT: Do not rotate the cannula while pulling it through the tunnel. At the end of this procedure, the apex of the heart should be in its native position without torsion.
4. Terminate ventricular fibrillation if necessary.

6.6 Atrial cannula(e)

Refer to section 6.2: Use of the cannula tunneling tip, page 57.

ADVICE

For atrial cannulae supplied with a forming wire, the transcutaneous tunnel should be created and the cannula advanced through the tunnel and skin incision prior to the anastomosis.
For all other atrial cannulae, the sequence is arbitrary.

6.6.1 Creating a transcutaneous tunnel for atrial cannula(e)

WARNING

If possible, always use the cannula tunneling tip provided (see section 6.2: Use of the cannula tunneling tip, page 57) to advance the cannula through the prepared transcutaneous tunnel.

If it is necessary to apply a clamp directly to the cannula in order to pull the cannula through the skin, the following procedures should be observed:
- Position the clamp at the distal end of the cannula
- After the cannula has been pulled through the skin, cut off and discard the part of the cannula where the clamp was applied.
- If it is necessary to clamp any other part of the cannula that is not covered with velour, cover the part of the cannula that will be clamped with a gauze sponge.

Care must be taken to ensure that the cannulae come to rest in a stable position free of tension.

Do not touch or manipulate the silicone cannulae with pointed or sharp-edged objects (e. g. surgical instruments).

Using a pair of forceps, firmly grip the flat end piece of the tunneling tip and pull it through the cannula tunnel and the skin incision.
IMPORTANT: Do not rotate the cannula while pulling it through the tunnel.

The incision must be slightly smaller than the cannula diameter (to ensure good ingrowth) but large enough to prevent necrosis.

Plan the cannula exit sites appropriately. Leave an adequate bridge of skin and subcutaneous tissue between the cannula exit incisions to prevent breakdown and necrosis of the skin and tissue. If possible the cannula exit in sic ions should be on different planes.

INSTRUCTION

1. Prepare the transcutaneous tunnel. Ensure that the incision is large enough.
2. Prepare the cannula tunnel by blunt dissection. IMPORTANT: Do not tunnel transperitoneally.
3. Using a pair of dressing forceps, tunnel the cannula through the transcutaneous tunnel. IMPORTANT: Do not rotate the cannula while pulling it through the tunnel.

6.6.2 Anastomosis of atrial cannulae

Right atrium

ADVICE

Create the anastomosis laterally, directly above the tricuspid valve.

a) closed technique

INSTRUCTION

1. Make a running (purse-string) suture with monofilament, secured with pledgets at 4 positions.
2. Place 4 single U-sutures secured with pledgets on each side of the purse string suture.
3. Make a sufficiently long incision inside of the suture circle and extend it as required.
4. Push the cannula down on the sutures, at the same time slightly reduce the venous inflow to the CPB while inflating the lung in order to prevent negative pressure in the left atrium.
5. Remove all air from the cannula and use a tube clamp to clamp the cannula below the anastomosis.

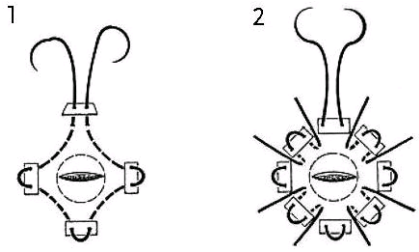


Fig. 6-9 Suture technique, right atrium

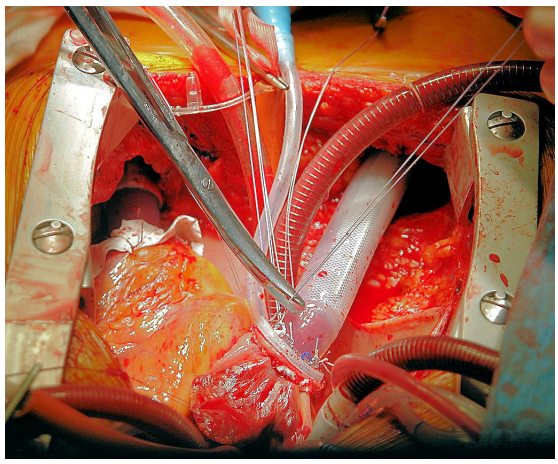


Fig. 6-10 Cannulation of right atrium

b) open technique with bicaval cannulation

With bicaval cannulation, the right atrial cannula can be inserted in an open technique.

Left atrium

The procedure for anastomosis of the left atrium corresponds to the procedure applied to the right atrium.

ADVICE

Place anastomosis at the junction of the right upper pulmonary vein and the left atrium. The atrial wall is the recommended implantation location. The pulmonary vein should be left intact.

6.7 Arterial cannula(e)

Refer to section 6.2: Use of the cannula tunneling tip, page 57.

ADVICE

For cannulae supplied with a forming wire, the transcutaneous tunnel should be created and the cannula advanced through the tunnel and skin ins cis ion prior to the anastomosis.

6.7.1 Creating a transcutaneous tunnel for arterial cannula

WARNING

Care must be taken to ensure that the blood pump and cannulae come to rest in a stable position.

Do not touch or manipulate the silicone cannulae with pointed or sharp-edged objects (e. g. surgical instruments).

Using a pair of forceps, firmly grip the flat end piece of the tunneling tip and pull it through the cannula tunnel and the skin incision. IMPORTANT: Do not rotate the cannula while pulling it through the tunnel.

The incision must be smaller than the cannula diameter (to ensure good ingrowth) but large enough to prevent skin necrosis.

Plan the cannula exit sites appropriately. Leave an adequate bridge of skin and subcutaneous tissue between the cannula exit incisions to pre-vent breakdown and necrosis of the skin and tissue. If possible the cannula exit insicions should be on different planes (see Fig. 6-2, page 56).

INSTRUCTION

1. Prepare the transcutaneous tunnel. Ensure that the incision is large enough.
2. Prepare cannula tunnel by blunt dissection. IMPORTANT: Do not tunnel trans-peritoneally.
3. Using a pair of forceps, firmly grip the flat end piece of the tunneling tip and pull it through the cannula tunnel and the skin incision. IMPORTANT: Do not rotate the cannula while pulling it through the tunnel.

6.7.2 Anastomosis of the arterial cannula

Aorta

INSTRUCTION

1. Tangentially clamp the ascending aorta and make a longitudinal opening of a length which is suitable for the cannula diameter. If necessary, offset the incision laterally to the right by up to 45°.
2. Anastomose the cannula using ten teflon-backed double-reinforced individual monofilament (e. g. 4-0 EB) U-sutures. (If simpler conditions are encountered, a running suture can be made instead.)
3. Remove all air from the cannula and use a tube clamp to clamp the cannula below the anastomotic site. If it is necessary to clamp any other part of the cannula that is not covered with velour, cover the part of the cannula that will be clamped with a gauze sponge.

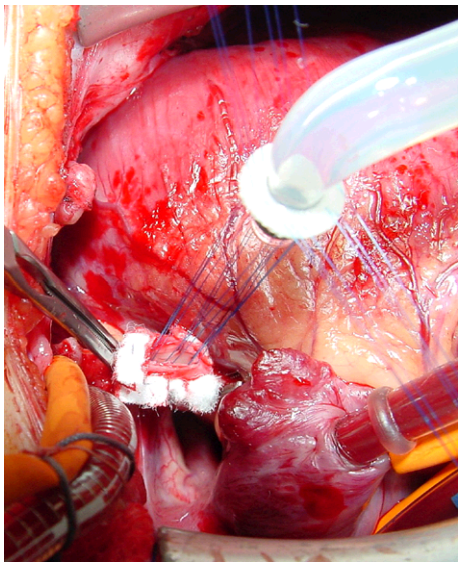


Fig. 6-11 Anastomosis of the aortic cannula

Pulmonary artery

INSTRUCTION

1. Make a longitudinal incision of a size suitable for the cannula diameter in the pulmonary artery.
2. Anastomose the cannula using 10 teflon-backed, double-reinforced individual monofilament (e. g. 4-0 EB) U-sutures. (If simpler conditions are encountered, a running suture can be made instead.)
3. Remove all air from the cannula and use a tube clamp to close it below the anastomosis. If it is necessary to clamp any other part of the cannula that is not covered with velour, cover the part of the cannula that will be clamped with a gauze sponge.

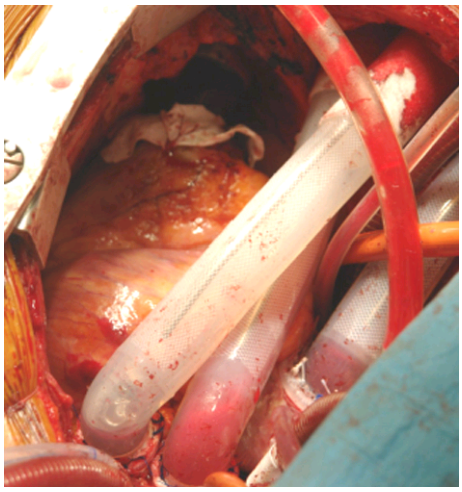


Fig. 6-12 Cannulation of the pulmonary artery

6.8 Shortening the cannulae if necessary

WARNING

If an EXCOR cannula extension set / connecting set is required for implantation and the length of the tube part needs to be reduced, the tube part should be cut but only to achieve the following minimum lengths:

Article	Diameter / Diameter reduction	Minimum length
Cannula extension set		
A06-006	6 mm	55 mm
A09-009	9 mm	60 mm
A12-012	12 mm	75 mm
Connecting set		
A06-009	9 to 6 mm	60 mm
A09-012	12 to 9 mm	75 mm

Tab. 6-2 Cannula extension set / connecting set: minimum length of tube section

INSTRUCTION

1. Cut the cannulae to the required length. Make the cut perpendicular to the cannula axis and ensure that the cut is straight.
2. Make sure that the lengths of the 2 cannulae leading to the same pump match. It must be possible to connect the cannulae to the pump without having to exert any tension.

6.9 Connecting the blood pumps to the cannulae

WARNING

Ensure that cannulae, blood pump(s) and driving tubes are not subject to external forces and are free of kinks or sharp bends.

When connecting the blood pump(s), pay attention to the direction of the arrows on the inflow and outflow stubs. These show the direction of the blood flow.

Type of support	Anastomosis of inflow cannula to	Points upwards...
Univentricular		
LVAD	apex	blood chamber
LVAD	atrium	air chamber

Tab. 6-3 Anastomosis and direction of the blood chambers

Type of support	Anastomosis of inflow cannula to	Points upwards...
Biventricular		
LVAD	apex	blood chamber
LVAD	atrium	air chamber
RVAD	atrium	air chamber

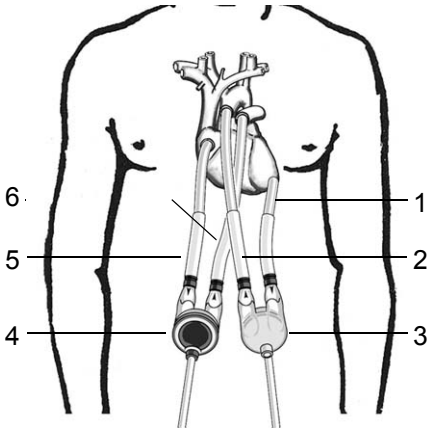
Tab. 6-3 Anastomosis and direction of the blood chambers

NOTICE

Finally, the driving tube is connected to the Ikus. The Ikus is started and the parameters are gradually adjusted (see section 6.10.4: Checking the parameters when the pump is started and adjusting them, page 71).

INSTRUCTION

1. Bring the patient into the Trendelenburg position.
2. Release the tube clamps, flush the cannulae and then use tube clamps to clamp the cannulae below the exit sites. If it is necessary to clamp any other part of the cannula that is not covered with velour, cover the part of the cannula that will be clamped with a gauze sponge.
3. First connect the inflow cannula to the pump, then connect the outflow cannula. When doing so, add sterile injectable saline with a bulb syringe in order to connect the pump air free. Be careful to avoid damaging the gloves and the inner cannula (lumen) and pump surfaces.
4. Release the tube clamps, de-air the pump(s) and the cannulae.
5. Connect the driving tube to the blood pump. Biventricular: use the red driving tube for the left blood pump and the blue driving tube for the right blood pump. Univentricular: always use the red driving tube.



1 inflow cannula from LV apex
2 outflow cannula to ascending aorta
3 left pump (blood-chamber pointing upwards)
4 right pump (air-chamber pointing upwards)
5 inflow cannula from right atrium
6 outflow cannula to pulmonary artery

Fig. 6-13 Final position of the blood pumps, for example: BVAD with LV apex cannulation

6.10 Intraoperative drive management

NOTE: This section omits safety instructions, information and procedures that refer to the Ikus exclusively. Please refer also to the IFU.

6.10.1 Connecting the blood pump(s) to the Ikus

WARNING

Do not kink either the driving tubes or the cannulae.

NOTICE

State of the blood pumps when they are initially connected: filled with sterile injectable saline, de-airing needle in place. To allow easier handling, the driving tubes are not connected until the inflow and outflow cannulae have been connected to the pump (see section 6.9: Connecting the blood pumps to the cannulae, page 68).

INSTRUCTION

1. Open the driving tube connector marked in red (univentricular) or both connectors (biventricular). To do so, pull the seal plugs out of the connector(s).
2. Connect the driving tube to the Ikus. To do so, push the plug of the driving tube into the connector. The sound of the plug snapping into place is clearly audible. Check that the plug is securely connected. To do so, grip the plug body above the release sleeve and pull on it. Do not pull from the release sleeve, and never from the tube!
3. In biventricular mode: observe the color of the markings.
4. In biventricular mode: repeat the procedure for the second pump.

Operating mode	Ikus connector
biventricular	LVAD: connector marked red RVAD: connector marked blue
univentricular	connector marked red

Tab. 6-4 Assignment: operating mode, blood pump, connector

6.10.2 De-airing the blood pumps in single-step mode

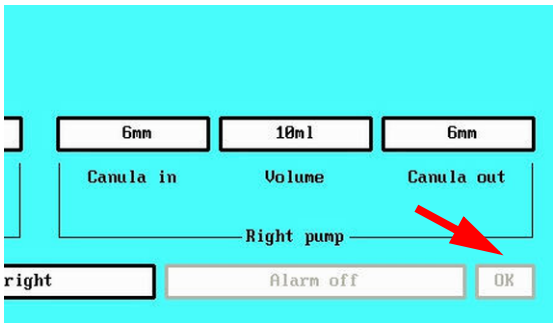
NOTICE

Each de-airing step (**Step left**/ **Step right**) carries out half a pump cycle (systole or diastole), the 1st step being a diastole. Normally, several de-airing steps are required for each pump. In single-step mode, the pumps will operate using the pressures shown in the parameter table. It will not be possible to switch to the standard view unless at least 1 de-airing step has been completed for each connected pump.

INSTRUCTION

1. Bring the patient into the Trendelenburg position.
2. Move the cursor to the field marked **Step left**.
3. Lift the pump. The de-airing nipple is the highest point.

4. To trigger a single step, press the **<Enter>** key. If necessary, use the de-airing needle to vent the air from the pump (see section 5.5: De-airing the blood pump, page 52). After consulting the surgeon: If necessary, press **<Enter>** repeatedly to trigger further single steps until all air has been removed from the pump(s). If the blood pump is not filling sufficiently, ensure there is sufficient preload and if necessary, increase the diastolic pressure.
5. In biventricular mode: Move the cursor to the field **Step right**. Repeat the procedure for the 2nd pump.



Transition to continuous pumping mode is not yet possible because **OK** field is still inactive.

Fig. 6-14 Single-step mode

6.10.3 Starting the blood pump (changing to standard view)

WARNING

Do not start the pump(s) until all air has been removed.

Once the de-airing needle has been removed it cannot be re-inserted.

Only remove the de-airing needle after all air has been removed from the blood pump, the blood pump is running and the parameters have been adjusted (see section section 6.10.4: Checking the parameters when the pump is started and adjusting them, page 71 and section 6.11: Removing the de-airing needle, page 76).

INSTRUCTION

1. Move cursor to the **OK** field and press **<Enter>** to confirm. The system now starts with the parameter values visible in the parameter table.

6.10.4 Checking the parameters when the pump is started and adjusting them

WARNING

In order to avoid air being sucked into the blood pump through the cannula anastomosis, adjust the parameters gradually. If air does enter the system, disconnect the driving tubes from the Ikus and de-air the system using the de-airing needle.

Continuously monitor all settings.

Once the de-airing needle has been removed it cannot be re-inserted.

NOTICE

If the pump is not filling adequately at this stage, increase the preload by adding volume from the CPB circuit. After adding volume, adjust the parameters on the laptop of the *Ikus* as described in the following table.

INSTRUCTION

1. Observe the left blood pump. Is the pump ejecting completely? If not: increase the left driving pressure if necessary.
2. Observe the right blood pump. Is the pump ejecting completely? If not: increase the right driving pressure if necessary.

Observe	Action / measure
Right pump Is the pump filling properly? (see below)	If not: check the filling pressure (central venous pressure; CVP) CVP too low: substitute volume CVP too high: increase suction pressure If no improvement occurs: check the position of the cannulae via echographic monitoring!
Left pump Is the pump ejecting properly?	If not: check mean arterial pressure (Guideline value: 70mmHg)
Compare left and right pump. Is left pump filling considerably worse than right pump?	If yes: increase suction pressure on left side If no improvement occurs: check the position of the cannulae via echographic monitoring!

Tab. 6-5 Pump filling criteria

Keep the following points in mind with regard to filling of the right pump:

The aim is to reduce the right ventricle's load to a large extent but not completely. Signs that the RV load has been reduced completely are:

- filling of the pump depends largely on the respiratory cycle
- ventricle is empty/limp
- membrane stops abruptly during filling

IMPORTANT: If the three above-mentioned phenomena are observed, do one of the following:

- reduce the diastolic pressure
- substitute volume

Adjusting parameters

INSTRUCTION

1. Use the **<←>/<→>** keys to move the cursor to the desired field in the parameter table. The selected field is given a colored background.
2. Use the **<↓>**,**<↑>** or **<Bild-↓>**, **<Bild-↑>** keys to adjust the value, then press **<Enter>** to confirm the input.

Parameter	Range possible	<↓>/<↑> changes value by	<Bild-↓>/<Bild-↑> changes value by
Systolic pressure [mmHg]; driving pressure	60 to 350	2.5	25
Diastolic pressure [mmHg]; suction pressure	0 to -100	2.5	25
Rate [bpm]	30 to 150	1	10
Relative systolic duration [%]	20 to 70	1	10

Tab. 6-6 Parameter's possible adjustments

In biventricular operation: adjusting the operating mode

To run the pumps in the asynchronous mode or separate mode instead of the synchronous mode the appropriate mode must be selected.

- asynchronous mode is recommended for patients who have a small thorax volume in comparison to the pump volume. In asynchronous mode, the intrathoracic blood volume remains unchanged.
- separate mode is useful, under some circumstances, for patients with intracardiac shunts.

INSTRUCTION

1. Use the **<←>/<→>** keys to move the cursor to the field showing the current operating mode. A pop-up menu showing the available operating modes is opened (see Tab. 6-4, page 70).
2. Select the desired operating mode with **<↓>**,**<↑>** and confirm with **<Enter>**. The system will now work in the selected mode.

Guideline values

The most important criteria when selecting drive parameters is that they ensure a good filling and emptying of the pump; the parameters must be set to achieve this goal.

NOTICE

The systolic driving pressure must be higher than the patient's physical systolic pressure. IMPORTANT: If the systolic duration (% systole) is reduced or if very small cannulae are used, it may be necessary in some cases to select a higher value than recommended here.

The actual driving pressures achieved are influenced by the diameter of the cannulae used.

The following values are merely guideline values; they may not be appropriate in each individual case

Systolic pressure [mmHg], left/ right	Diastolic pressure [mmHg], left/ right	Rate [bpm]	Rel. systolic duration [%], left/ right
220/150	-40/-40	80	40/40

Tab. 6-7 Recommended guideline values for normal operation

ADVICE

Remove the de-airing needle after all air has been removed from the blood pump, the blood pump is running and the parameters have been adjusted (see section 6.10.4: Checking the parameters when the pump is started and adjusting them, page 71 and section 6.11: Removing the de-airing needle, page 76).
IMPORTANT: Once the de-airing needle has been removed it cannot be re-inserted.

6.10.5 Switching from CPB support to VAD support

The aim here is to reduce the CPB flow and in doing so to shift the volume from the CPB to the patient (i.e. to the VAD)

WARNING

Secure the driving tubes and cannulae to the blood pump(s) as soon as the proper function of the EXCOR is established (see section 6.12: Securing the connections, page 76).

INSTRUCTION

1. When the blood pump(s) starts to fill, reduce the CPB flow and gradually increase the EXCOR rate from an initial 30 bpm until CPB has been terminated and the required flow is achieved. IMPORTANT: In doing so, make sure that the pump fills adequately, and if necessary regulate the driving pressure.
2. If necessary, adjust the systolic pressure, diastolic pressure and the systolic percent.

6.10.6 Possible complications

Decreased filling after stable filling conditions

If a good filling behavior was achieved at first (filling pressures LA/CVP < 10 mmHg and diastolic pulmonary artery pressure < 15 mmHg) with good drainage and nominal rate (normally 80 bpm), but the filling has deteriorated over time, it usually will not help to increase the diastolic pressure.

Deterioration in the filling behavior despite stable inflow conditions may indicate hypovolemia or obstruction of the inflow cannula. The cause of deterioration in filling behavior must be identified and addressed.

NOTICE

Manipulations during implantation can severely influence the inflow temporarily – wait for the situation to stabilize before adjusting the values.

INSTRUCTION

1. Evaluate volume status and transfuse if necessary. Evaluate and if necessary correct the cannula position.

Pump filling deteriorates when thorax is closed

If atrial cannulation is used, a slight decrease in the filling may be observed in some cases when the thorax is closed. This may be caused by compression of the atria or a slight shift in the position of the cannulae.

INSTRUCTION

1. Evaluate volume status and transfuse if necessary. IMPORTANT: Observe the effect volume replacement on the pump filling!
2. Increase suction pressure.

Distinct decrease in filling or generally poor inflow conditions on right side

INSTRUCTION

1. Make sure that there is no inflow obstruction.
2. If a suction pressure of less than -50 mmHg is necessary, increase the relative diastolic duration as an additional measure. At the same time, reduce the relative systolic duration. IMPORTANT: Increase the driving pressure accordingly!

Incomplete ejection right/left

INSTRUCTION

1. Observe the arterial blood pressure, and at the same time observe the ejection movement of the pump membrane.
2. If complete emptying of the pump is no longer achieved, adjust the driving pressure accordingly. IMPORTANT: Do not respond to extreme – temporary – increases in the arterial blood pressure (due to manipulation, catecholamine, etc.).

6.11 Removing the de-airing needle

WARNING

When removing the de-airing needle, never pull on the de-airing tube, but on the de-airing needle itself.

Before removing the de-airing needle, be sure that the de-airing tube is secured to the de-airing needle. IMPORTANT: Once the de-airing needle has been removed it cannot be re-inserted.

NOTICE

Do not remove the de-airing needle until all air is removed, the blood pump is running, all parameters have been adjusted and the chest has been closed. (see section 6.10.4: Checking the parameters when the pump is started and adjusting them, page 71).

INSTRUCTION

1. Cut the suture material between the de-airing needle and the de-airing nipple (see image 1 in Fig. 6-15, page 76). IMPORTANT: Leave the ligature around the de-airing nipple (see image 2 in Fig. 6-15, page 76).
2. Pull the de-airing needle out of the de-airing nipple.

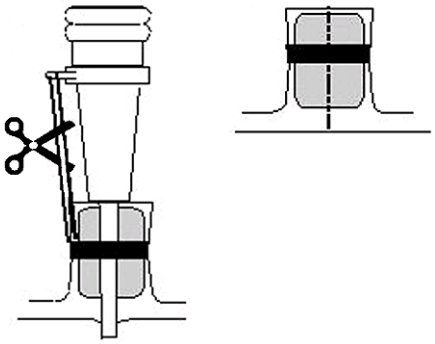


Fig. 6-15 Removing the de-airing needle

After the patient has been weaned from the CPB and the proper function of the EXCOR is established, the connections of the driving tubes and cannulae to the blood pump(s) have to be secured.

6.12 Securing the connections

WARNING

All connections have to be secured by at least 1 cable tie. 2 cable ties may be used. Exception: connection between drive line and drive line connector of the blood pump: 1 cable tie only!

INSTRUCTION

1. Pick up the Tube connecting set.
2. Secure the following connections:
   - inflow cannula on the connector of pump / cannula extension set / connecting set
   - outflow cannula on the connector of pump / cannula extension set / connecting set
   - cannula extension set / connecting set on the connector of the pump
   - drive line on the drive line connector (1 cable tie only!)

3. The 1st cable tie must be positioned exactly on the groove profile of the connector (*1*).
   IMPORTANT: the heads of the cable ties have to be directed away from the patient's body.
4. Fasten the cable ties by the cable tie gun. IMPORTANT: pay attention to section 5.2: Checking and adjusting the settings of the cable tie gun, page 49.
5. A 2nd cable tie can be used optionally. If a 2nd cable tie shall be used (*2*) it has to be positioned above the 1st cable tie. IMPORTANT: the heads of the cable tie straps should both be staggered and directed away from the patient's body.

Fig. 6-16 Cable tie, exactly positioned

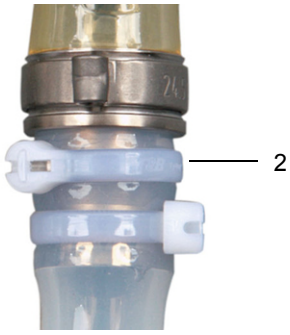


Fig. 6-17 2nd cable tie (optional)

6. If an EXCOR cannula extension set / connecting set is required for implantation after that secure also those connections with cable ties. Proceed thereby as described in the instruction steps 3 to 5.

6.13 Postoperative drive management

NOTICE

The patient should receive the same treatment as is usual after any other major cardiac surgical procedure.

6.13.1 After transfer to the ward

If a good filling and stable ejection of the blood pump(s) is observed in the immediate post-operative period, it is normally not necessary to adjust the driving and suction pressures.

- Good filling means that the suction pressure is adequate.
- Stable ejection (at normal arterial blood pressure) means that the driving pressure is adequate.

⚠ WARNING

At least every 4 hours, visually check that the pump(s) is (are) filling and ejecting completely over a period of several pump cycles. If a pump is not filling and/ or ejecting completely, appropriate measures are to be taken.

NOTICE

For further details on regular monitoring of pump(s) and cannulae, see section 8.5: Regular checks of blood pump(s) and cannulae, page 87.

6.13.2 Follow-up treatment

Guideline values and criteria for adjusting the parameter settings: see Tab. 6-7, page 74.

It is only necessary to adjust the left driving pressure when

- the arterial blood pressure increases (e. g. after lifting sedation, when the patient wakes up)
- when the patient is mobilized (moving to an upright position, sitting, standing – in order to compensate for the additional hydrostatic pressure component).

7 Implantation - anesthesia

The following risk factors should be closely monitored for anesthetic and hemodynamic management:

- right heart function during LVAD implantation
- coagulopathy
- renal insufficiency
- abnormal reactions to inotrope administration
- pulmonary hypertension

CAUTION

There should be an adequate supply of pre-matched stored blood, fresh frozen plasma and platelet concentrates available for immediate transfusion if required.

Keep blood product transfusions to a minimum. Blood transfusions may lead to the development of antibodies, which are known to promote coagulation and inflammatory response.

ADVICE

Medication for right ventricular afterload reduction should be available for use in the operating room (nitric oxide NO, phosphodiesterase inhibitor, prostaglandin, etc)

Auto-transfusion equipment (e. g. Cellsaver) should be available for use in the operating room.

For patients with an LVAD, start ventilation with nitric oxide or administer the appropriate medication to treat pulmonary hypertension and reduce afterload for right ventricle 15 minutes before weaning from the CPB. This can help to prevent or lower the risk of right ventricular failure.

Monitoring procedure

Intraoperative monitoring should include the same monitoring procedures applied during major cardiothoracic surgery:

- central venous line
- Swan-Ganz catheter (if appropriate)
- arterial line
- ECG
- pulse oximetry
- central temperature monitor
- urine catheter

Additional recommended monitoring procedures

- cardiac output calculation (if appropriate)
- intraoperative transesophageal echocardiogram (inflow cannula position, heart valve function, intracardial shunts, volume status
- right heart function in case of LVAD

Any other monitoring processes can be used (e. g. neurological monitoring) at the anesthesiologist’s discretion.

8 Wound care and treatment

Cannula exit sites should be treated like open wounds. The patient's wounds should always be attended to by a small group of nurses in the inpatient area.

The only way to ensure there is a minimum risk of infection is to provide good wound care.

WARNING

Before cleaning the wound (see section 8.3: Cleaning of the wound, page 83), put on sterile disposable gloves, cap and mask.

Cleaning the pump and the drive line: Do not use any acetone or petroleum based products near the pump or drivelines.
We recommend using only water or alcohol to clean the pump and the drive line.
IMPORTANT: Do not use any corrosive or colored solutions or organic solvents to clean the blood pump or the drive line as they may alter the surface of the product.

Cleaning the cannulae and transcutaneous exit site: Do not use any acetone or petroleum based products near the cannulae and the transcutaneous exit site.
We recommend using chlorhexidine to clean the cannulae and transcutaneous exit site.
IMPORTANT: Do not use any corrosive or colored solutions or organic solvents to clean the cannulae and the transcutaneous exit site as they may alter the surface of the product.

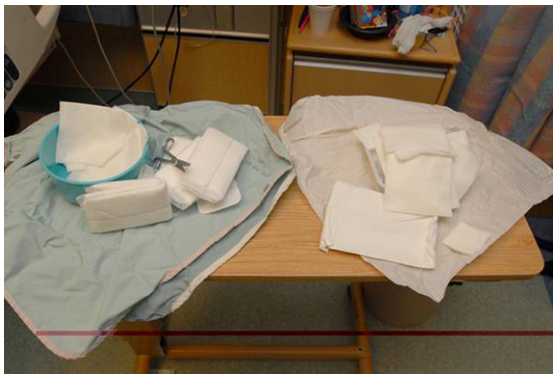
NOTICE

Do not stick bandages to the cannulae. Over time, remnants of adhesive contaminate the cannulae and increase the risk of infection.

Do not use any adhesive on the velour coating of the cannula as it is difficult to remove and may adversely manipulate the cannula.

Do not use organic solvents near the EXCOR Pediatric such as petroleum ether or turpentine oil, as they could damage the cannulae and the pumps. The plastic parts must not get in contact with chlorinated hydrocarbon (e.g. chloroform), thinners (e.g. acetone, naphtha, toluol, xylene, heptane) or similar compounds.

Do not mark or write on the plastic parts.



Material required (with biventricular access):

- Sterile dressing tray
- Disinfectant i.e. 2% chlorhexidine solution
- Clean gloves
- Mask
- Sterile gloves and towel
- *Metalline*® drain compress
- 2X2 gauze, 4X4 gauze
- Adhesive dressing (i.e. *Mepore*®)
- Adhesive remover
- Non sting barrier film sticks
- Abdominal pads
- Tape
- Tubular bandage (i.e. *Burnnet*)

Fig. 8-1 Materials for dressing change

How often to change the dressing

If the wound is dry and not infected:

- POD 1- once a day
- POD 11-28 every second day, if the wound is dry and not infected
- POD>28 twice a week, if the wound is dry and not infected

If the wound shows signs of infection: clean wound and change dressing twice a day

8.1 Removing the old dressings

INSTRUCTION

1. Unpack all the material required to dress the wound and place this within reach on a sterile sheet.
2. Put on disposable gloves, remove old dressings.
3. Take off the disposable gloves, put on the sterile gloves.
4. Remove old dressing using no-touch technique.
5. Examine the places where the cannulae pass through the skin and if changes are apparent take appropriate measures if necessary.
6. Use adhesive remover to remove any adhesive dressing.
   IMPORTANT: adhesive remover (depending on contents) might damage cannula and the pump, use only on skin.

8.2 Cleaning the blood pump

INSTRUCTION

1. Cleanse the exposed cannula and the pump head with disinfectant (i.e. 2% chlorhexidine solution) then place on sterile towel.
2. Examine cannulae and cannulae exit sites.
3. Remove gloves.

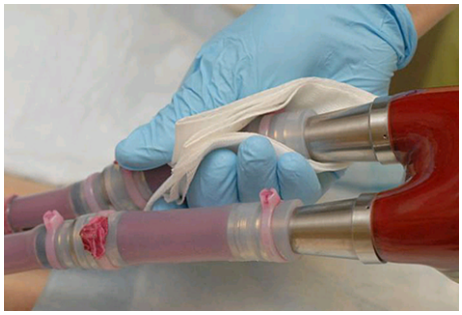


Fig. 8-2 Cleaning the blood pump

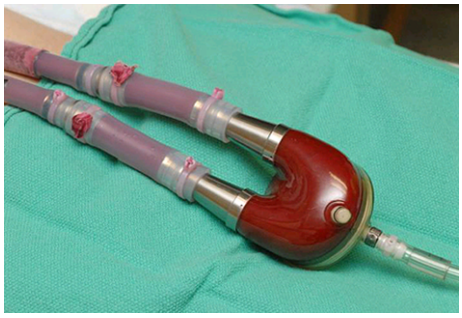


Fig. 8-3 Examining the cannulae

8.3 Cleaning of the wound

INSTRUCTION

1. Hand hygiene, prepare sterile dressing tray, put on sterile gloves. If assistance is necessary notify Berlin Heart.
2. 4X4 gauze soaked in 2% chlorhexidine cleanse each cannula exit site in a circular motion outward to a radius of approximately 10 cm.
3. Using a new soaked 4X4 repeat 2 more times beginning at the exit site and clean in larger circles each time.
4. Wrap 4X4 gauze soaked in 2% chlorhexidine around cannula and gently cleanse with back/forth motion.
5. Repeat with each cannula exit site.

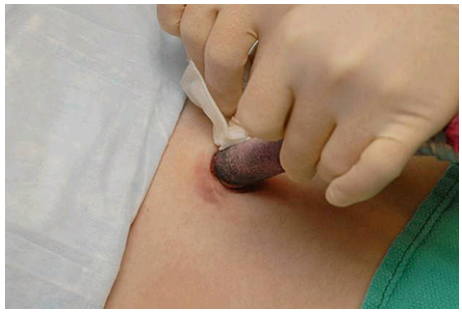


Fig. 8-4 Cleanse each cannula exit site

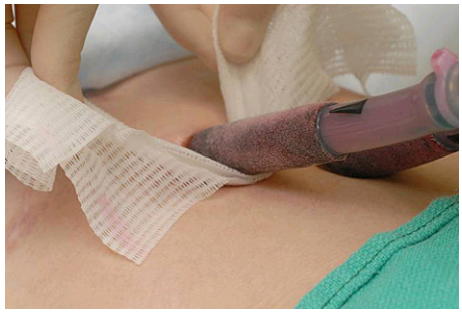


Fig. 8-5 Cleanse with back/forth motion

6. Cleanse entire cannula (upper and bottom side).
7. 4X4 gauze soaked in 2% chlorhexidine solution.
8. Starting at the exit site moving down cannula approximately 10 cm from exit site.
9. Repeat for each cannula exit site.
10. Allow chlorhexidine to dry completely.

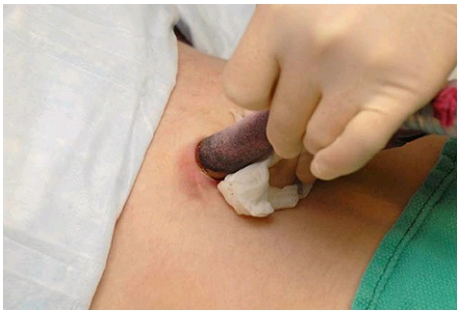


Fig. 8-6 Cleanse entire cannula

8.4 The new dressing

8.4.1 Preparing a new dressing

INSTRUCTION

1. Apply non sting barrier film to skin around cannulae. Non sting barrier prevents skin maceration around cannula exit sites.

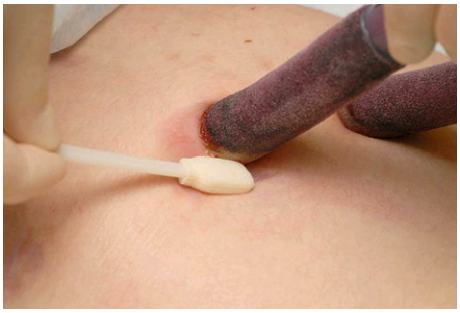


Fig. 8-7 Non sting barrier film

8.4.2 Applying a new dressing

INSTRUCTION

1. Wrap a *Metalline* drain compress around each cannula (from right to left, slit always facing upwards).

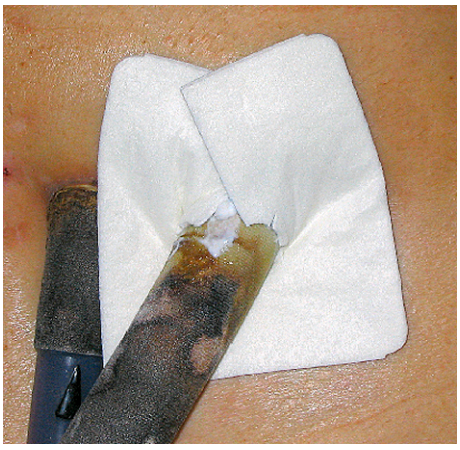


Fig. 8-8 Metalline drain compress

2. Attach the *Metalline* drain compresses above the cannulae using sterile bandages. First secure the outer compresses, then the inner compresses.

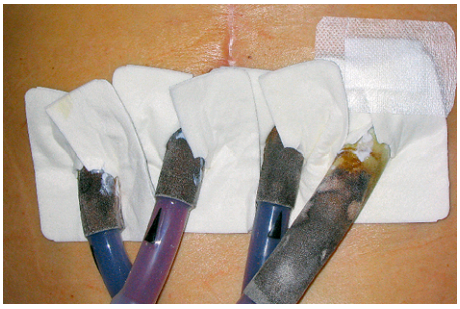


Fig. 8-9 Secure with a sterile bandage

3. Pass a gauze compress folded lengthwise beneath the 2 left cannulae. The open end of the folded compress should point in the direction of the wound. Pull the cannulae into place by tugging the compress slightly.

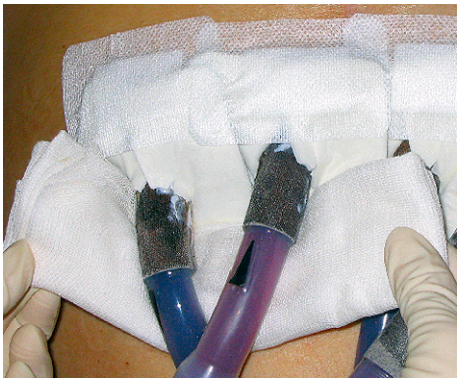


Fig. 8-10 Gauze compress under the cannulae

4. Fold the left end of the compress upwards, diagonally to the right and secure with a sterile bandage .

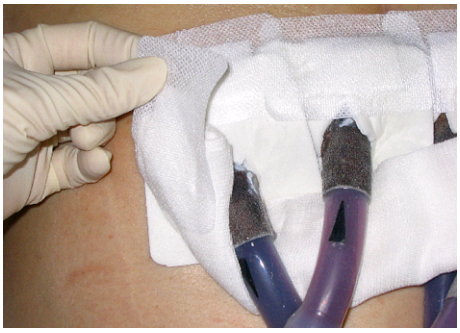


Fig. 8-11 Fold the left end of compress and secure

5. Fold the right end of the compress upwards, diagonally to the left and secure with a sterile bandage.

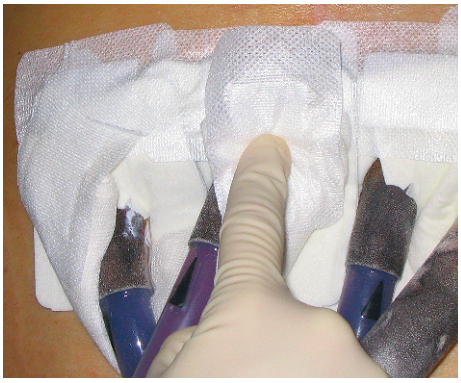


Fig. 8-12 Fold the right end of compress and secure

6. Repeat this procedure for the 2 right cannulae. In this way, the 4 cannulae are padded so that they do not press on the skin or wound.

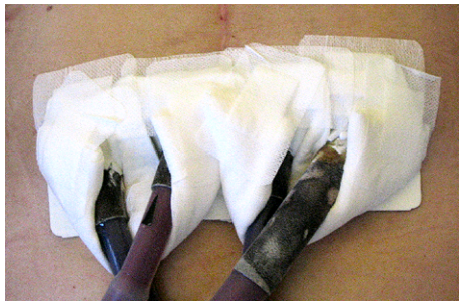


Fig. 8-13 Cannulae are padded

7. Cover the entire wound broadly with gauze compresses.

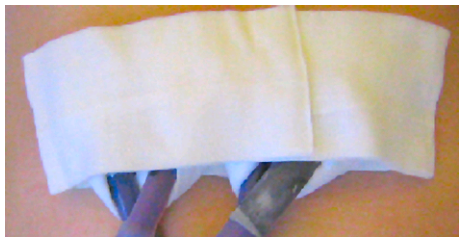


Fig. 8-14 Cover with sterile gauze compresses

8. Secure the upper part of the dressing with a sterile bandage.

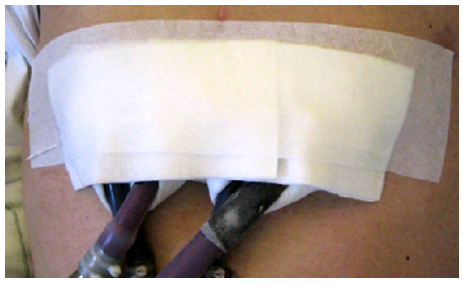


Fig. 8-15 Secure with a sterile bandage

9. Finally, seal the dressing at the left and right side, below the cannulae and between the individual cannulae with strips of adhesive bandage (e. g. Leukoplast).

Fig. 8-16 Seal with strips of adhesive bandage

10. Place tubular bandage (i.e. *Burnnet*) around patient.
11. Tie in front to secure dressing.

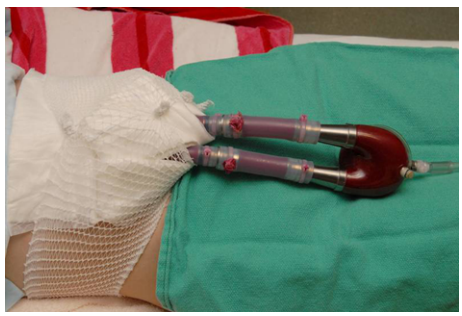


Fig. 8-17 Tubular bandage

8.5 Regular checks of blood pump(s) and cannulae

Frequency of inspection: every 4 hours

WARNING

Everyone involved in caring for an EXCOR patient must be trained to carry out a visual check, to evaluate the filling behavior of the blood pump(s) and to detect deposits.

CAUTION

At least daily, the EXCOR cannulae should be inspected for signs of wear or damage. ADVICE: To avoid needless kinking of the cannulae use a mirror for inspection of the bottom side of the blood pump.

Educate the patient, family and caregiver to avoid pulling, kinking or any activity that could put stress on the cannula. Remind them periodically of the importance of protecting the cannnula and blood pump. Do not allow patient to belly flop, pull or stretch the cannula, as this may damage the cannula resulting in injury or death to the patient.

At least every 4 hours, check visually that the blood pump(s) is (are) filling and ejecting completely over a period of several pump cycles. If a pump is not filling and/ or ejecting completely, then take the appropriate corrective action.

8.5.1 Visual inspection: pump filling and ejection

The filling and ejection behavior of a blood pump is optimal when the membrane surface is completely smooth at the end-of-systole and end-of-diastole positions. Check visually that the pump(s) is (are) filling and ejecting completely over a period of several pump cycles. If a pump is not filling and/ or ejecting completely, take the appropriate corrective action.

Cautionary measures

For all blood pumps: check the position and condition of the driving tube and the cannulae (inflow deterioration due to kinks in cannulae/driving tubes is rather rare).

For all blood pumps: check the membrane movement.

Medical examination of patient

Check CVP, mean arterial pressure and adjust therapy if necessary.

Check the volume status:

- amount of bleeding
- increased urine output (use of diuretics?)
- tamponade
- IMPORTANT: Increasing the suction pressure will not bring about any distinct improvement if there is not sufficient volume available.

LVAD: observe the functions of the right ventricle.

Adjusting the parameter values

Only adjust the parameters if the measures listed above have no effect or in case of:

- Mobilization of patient: adjust the systolic pressure, both left and right. When pressures have increased, do not reduce these again, even when the patient is lying down.
- Signs of low cardiac output: the membrane is moving properly while at the same time a decrease in urine output, lactate increase and dyspnea (shortage of breath) can be observed. In this case, increase the rate and adjust other settings as required.

INSTRUCTION

1. Use the **<←>/<→>** keys to move the cursor to the desired field in the parameter table. The selected field is given a colored background.
2. Use the **<↓>**,**<↑>** and **<Bild-↓>**, **<Bild-↑>** keys to adjust the value, then press **<Enter>** to confirm the input. The system will now operate using the new settings.

Cautionary measure

Confirm each changed parameter value by pressing **<Enter>**. The system does not take over the new, changed value until it has been confirmed with **<Enter>**.

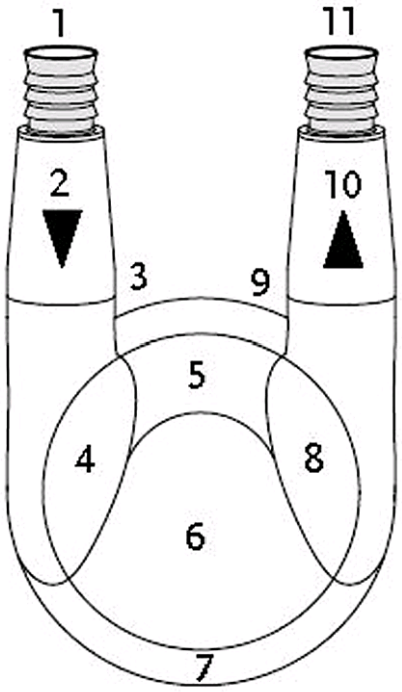
ADVICE

Enter all the changes to the parameter values into the parameter log. (see section 12.7: Pump performance flow sheet, page 148).

8.5.2 Visual inspection: deposits

Check the blood pump(s) and the visible part of the cannulae (cannula extension set / connecting set resp.) for visible deposits (fibrin, clots) every 4 hours. If deposits develop, check the pump(s) every hour.

Checking the pump areas which come in contact with blood



1 transition inflow cannula – inflow connector
2 inflow stub in front of inflow valve
3 inflow valve
4 inflow stub behind inflow valve
5 area between inflow and outflow stubs
6 remaining area of blood chamber
7 transition blood chamber - membrane (directly above the reinforcement ring)
8 outflow stub in front of outflow valve
9 transition outflow connector – outflow cannula
10 outflow valve
11 outflow stub behind outflow valve

Fig. 8-18 Diagram of EXCOR blood pump (top view of blood chamber)

ADVICE

During the visual check, first clean the blood pump then illuminate the blood chamber with a flashlight. This makes it easier to detect deposits. Enter all of the findings into the blood pump log. (see section 12.6: Sample copy: EXCOR pump log, page 145).

Cautionary measures

Initial signs of deposits: check anticoagulation therapy and adjust therapy if necessary.

Floating deposits inside the pump: replace the pump!

8.5.3 Checks using the monitor program

Record all drive parameters and adjust if necessary.

Objective: the blood pump(s) must fill and eject completely in each pumping cycle, the diastolic pressure should be as low as possible.

ADVICE

Record the parameter values once a day.

To record the parameters use the sample copy in section 12.7: Pump performance flow sheet, page 148.

8.5.4 Replacing the blood pump due to growth of the patient

CAUTION

In children, plan to replace the pump(s) with a larger pump(s) in good time, to prevent the possibility of inadequate support due to an insufficient discharge rate.

The pump selected at the time of transplantation may not be adequate for the entire period of cardiac support. Growth and/or weight gain can result in the patient not receiving adequate support. Use the chart in section section 12.1.2: Overview: Relationship: body weight – pump size, page 129, to plan, in good time, which pump(s) the patient may need to change over to. This chart is for guideline purposes only and is not binding for each individual case. This decision must be taken by the surgeon in consultation with Berlin Heart GmbH.

HOTLINE

Notify Berlin Heart! 866.249.0128

The blood pump(s) must be replaced as described in section 10.1: Replacing the blood pump(s), page 103.

9 Anticoagulation therapy

9.1 Before Implantation of the EXCOR

9.1.1 General considerations

Patients with an EXCOR system must be maintained on anticoagulation therapy.

Anti-Xa levels should be specific to the drug being used, either unfractionated heparin or enoxaparin.

The TEG® may be useful in managing unfractionated heparin and antiplatelet therapy. Please contact Berlin Heart, Clinical Affairs for further information.

9.1.2 Pre implantation

The following laboratory tests should be considered prior to implantation.

- Platelet Function Studies, INR, PTT, fibrinogen, antithrombin III, and platelet count to establish a baseline. Assessment for thrombophilia by measuring Protein C, S, Factor V Leiden, Prothrombin 20210 defect, as well as Heparin Induced Thrombocytopenia (HIT) is recommended.

9.2 During Implantation - Cardiopulmonary Bypass

9.2.1 Cardiopulmonary Bypass (CPB)

Use unfractionated heparin as per institutional protocol for cardiopulmonary bypass.

9.2.2 Post CPB

Completely reverse heparin with protamine sulphate as per institutional protocol.

The goal post-CPB is to achieve normal (institution specific) coagulation parameters (INR, PTT, fibrinogen, platelet count).

In the early post-operative period, the possibility of surgical bleeding, GI bleeding, internal bleeding in the retro-peritoneum or other bleeding diathesis is possible and must be monitored.

If the patient is bleeding despite normal coagulation parameters consider:

- Von Willebrand's
- Surgical bleeding

9.3 Postoperative anticoagulation therapy

9.3.1 General Considerations

Primary tests used to evaluate anticoagulation in the patient include antifactor Xa levels and/or PTT.

9.3.2 Starting anticoagulation therapy

During the first 24 hours following implantation, no anticoagulants should be administered.

Approximately 24 - 48 hours after implantation, commence unfractionated heparin therapy (i.v.) if the following criteria are met:

- Platelet count >20,000/µl
- Normal Platelet Function Studies
- Minimal bleeding in infants and young children.

9.3.3 Unfractionated heparin therapy (i.v.) Patient < 12 months

- Initial dose 15 IU/kg/hour.
- Do not use a bolus
- After 6 hours if the patient does not have increased bleeding, increase the heparin infusion to 28 IU/kg/hour (therapeutic dose).

6 hours after increasing the heparin to the therapeutic dose, obtain a PTT and an antifactor Xa level.

If the anti factor Xa level is desired range (0.35-0.5 U/ml) and the PTT is in the therapeutic range (institution dependent), then either the PTT or anti factor Xa level may be used to follow the heparin therapy.

If the anti factor Xa level is <0.35 U/ml or >0.5 U/ml, increase or decrease the heparin infusion, respectively until the anti factor Xa level is the therapeutic range (see Tab. 9-1, page 96).

Anti factor Xa levels should be obtained daily. IMPORTANT: hyperbilirubinemia may result in falsely low anti factor Xa levels. If anti Xa levels do not correlate with the PTT in this setting, consider using the PTT to monitor heparin therapy.

Antithrombin should be >70%. If the antithrombin is <70%, treat according to institutional protocol.

9.3.4 Unfractionated heparin therapy (i.v.) Patient ≥ 12 months

Initial dose 10 IU/kg/hour.

Do not use a bolus.

After 6 hours if the patient does not have increased bleeding, increase the heparin infusion to 20 IU/kg/hour (therapeutic dose).

6 hours after increasing the heparin to the therapeutic dose, obtain a PTT and an anti factor Xa level.

If the anti factor Xa level is desired range (0.35-0.5 U/ml) and the PTT is in the therapeutic range (institution dependent), then either the PTT or anti factor Xa level may be used to follow the heparin therapy.

If the anti factor Xa level is < 0.35 U/ml or > 0.5 U/ml, increase or decrease the heparin infusion, respectively until the anti factor Xa level is the therapeutic range (see Tab. 9-1, page 96).

Anti factor Xa levels should be obtained daily. IMPORTANT: hyperbilirubinemia may result in falsely low anti factor Xa levels. If anti Xa levels do not correlate with PTT in this setting, consider using the PTT to monitor heparin therapy.

Antithrombin should be >70%. If the antithrombin is <70%, treat according to institutional protocol.

NOTICE

If during standard unfractionated heparin therapy:
1. Platelet count is < 40,000/µl revert to the Stage I heparin dose for continuous infusion (see Tab. 9-1, page 96)
2. Platelets <20,000/ul discontinue heparin and consider evaluation for heparin induced thrombocytopenia (HIT).

If the anti factor Xa or PTT is too low or too high during heparin therapy, never use a bolus of heparin or protamine. Instead, increase or decrease the heparin dose, IU/hour, as required (see Tab. 9-1, page 96).

9.3.5 Thrombelastography (TEG®)

TEG® analysis may be useful in managing the anticoagulation and anti-platelet therapy. Please contact Berlin Heart Inc., Clinical Affairs for further information.

9.4 Low Molecular Weight Heparin

At 48 hours following surgery if all bleeding has stopped, the creatinine is within normal limits, and the patient is hemodynamically stable, switching from unfractionated heparin to low molecular weight heparin (LMWH) is recommended.

- Patient < 3 months start administration of Enoxaparin at 1.8 mg/kg subcutaneously every 12 hours.
- Patient > 3 - 12 months start administration of Enoxaparin at 1.4 mg/kg subcutaneously every 12 hours.
- Patient > 1 – 5 years start administration of Enoxaparin at 1.2 mg/kg subcutaneously every 12 hours.
- Patient > 5 – 16 years start administration of Enoxaparin at 1.1 mg/kg subcutaneously every 12 hours.
- Stop heparin infusion and administer LMWH (subcutaneously) simultaneously.
- Obtain the first anti factor Xa level at 4 hours after the 2nd LMWH dose is administered. See Tab. 9-2, page 96 for monitoring and dosing.
- Anti factor Xa therapeutic range: 0.6 to 1.0 U/ml.
- Anti factor Xa should be monitored along with platelet count, and creatinine
- When using LMWH, monitor Anti factor Xa daily. Once the Anti Factor Xa level is in the therapeutic range at a stable dose, monitor twice a week for 2 weeks, and then weekly.

9.5 Oral Anticoagulation Therapy (only for patients ≥ 12 months of age who are taking a full oral diet)

ADVICE

This section only applies to patients ≥ 12 months. Oral anticoagulation in children < 12 months of age is not recommended due to difficulties with monitoring the warfarin effect.

When the patient's condition has been fully stabilized (e.g. hemodynamically stable, no evidence of bleeding, etc), switch to oral anti-coagulation therapy with a vitamin K antagonist (target INR: 2.7 to 3.5), with an initial loading dose of 0.2 mg/kg/day. Do not exceed maximum loading dose of 5mg/day. The INR must be checked daily in the first

4 weeks, twice a week for the next 4 weeks (if INR is stable), and once a week there after (see Tab. 9-3, page 97 and Tab. 9-4, page 97.

Until the target INR is achieved, simultaneous administration of warfarin and heparin is necessary (approximately 4 days). Once the target INR is achieved, heparin therapy can be discontinued. If the INR decreases to < 2.7, administer LMW heparin immediately and then q12h until an INR of ≥ 2.7 is achieved (see Tab. 9-5, page 97). If INR is 2.0- 2.7 use an enoxaparin dose of 0.5 mg/kg targeting an anti factor Xa level of 0.3-0.5, if INR is <2.0 use an enoxaparin dose of 1 mg/kg targeting an anti factor Xa level of 0.5 - 1.0.

When unable to achieve a stable INR with warfarin, LMWH should be used instead. Discontinue the warfarin and administer LMWH as per previously discussed age related dosing (see Tab. 9-2, page 96).

9.6 Monitoring of Blood Count and Anticoagulation Status

Monitoring the anticoagulation status as well as infection risk, and renal and hepatic function is important and should be monitored with the following frequency:

- Daily while on UFH, twice a week while on enoxaparin/coumadin for 4 weeks then once week: Fibrinogen, D-dimer, aPTT, PT/INR, Platelet Count, TEG®, Antithrombin, WBC, HgB, HCT, BUN/SCr, AST/ALT, bilirubin T/D, prealbumin, CRP.
- While on UFH obtain anti factor Xa level daily.
- While on enoxaparin obtain anti factor Xa daily until in therapeutic range and on a stable dose, then twice a week for two weeks and then weekly.

If infection is suspected, appropriate measures must be taken immediately (antibiotic therapy, adjustment of the anticoagulation and platelet inhibition therapy) and increased monitoring of the coagulation system. In addition, in the setting of hemodynamic instability, organ dysfunction, and inadequate anticoagulation daily monitoring should be performed until any of these issues are resolved.

9.7 Postoperative platelet inhibition therapy

As individual patient responses vary to the anti-platelet agents, the optimum dosage for each patient will be that which minimizes both the risk of thromboembolic complications when the dose is too low and the risk of hemorrhagic complications when the dose is too high. Acetylsalicylic acid (ASA) and dipyridamole are the anti-platelet agents recommended.

9.7.1 Start of therapy

Dipyridamole

At 48 hours after surgery, start dipyridamole, 4mg/kg/day p.o. divided into 4 doses (1 mg/kg Q6) (maximum dose 15mg/kg/day). If the following are present:

- All bleeding has stopped, AND
- The patient is hemodynamically stable AND,
- Platelet studies do not show significantly decreased function,
- Platelet count is > 40,000/µl

Acetylsalicylic Acid

At 4 days post implantation, following the removal of all drainage tubes, start acetylsalicylic acid (ASA) 1mg/kg/day p.o., divided into 2 doses (0.5 mg/kg Q 12), if the following are present:

- Platelet studies show platelet inhibition in the presence of AA < 70 %

The ASA dose should split and be administered two times daily (0.5 mg/kg Q 12) due to the short half life and the high turnover of the platelets (approximately 10 % new platelets per day).

9.8 Adjunctive Medication

The inflammation parameters (Tissue factor pathway inhibitor, prothrombin fragment 1-2, fibrinogen, Factor VIII) for patients on ventricular assist device support are often elevated above normal. Accordingly, the physician may choose to administer the following medications at his/her discretion to facilitate the overall anticoagulation/anti-platelet management of the patient:

- Omega-3 fatty acids (e.g. DHA/EPA), have been shown to have an anti-inflammatory effect and also decrease premature activation of platelet membrane. Omega-3-fatty acids are composed of long chain polyunsaturated long chain carbons. Only alpha-linolenic acid (ALA) of the omega-3 family is truly essential.

Antioxidants (Vitamin C and E) also have been shown to have an anti-inflammatory effect, and may be considered.

9.9 Anticoagulation Therapy

9.9.1 Therapeutic Heparin administration and adjustment

NOTICE

This table assumes the site therapeutic PTT is 60 to 85 seconds (Monagle, P, et al.). Each site should use their hospital calculated therapeutic range.

Stage	Description	Anti factor Xa [u/ml]/PTT	Infusion	Hold heparin	Rate Change [%]	Repeat PTT
I	Initial Dose (first 6 hours)					
	Infant < 12 mo		15 IU/kg/h			
	Child ≥12mo		10 IU/kg/h			
II	Therapeutic Dose					
	Infant < 12 mo		28 IU/kg/h			after 6h
	Child ≥12mo		20 IU/kg/h			after 6h
III	Adjustment					
		<0.1/<50	0	0	+15%	4h
		0.1-0.34/ 50-60	0	0	+10%	6h
		0.35-0.50/ 60-85	0	0	0	next day
		0.51-0.70/ 86-95			-10%	6h
		0.71-0.89/ 96-120		30 min.	-10 %	4h
		= 0.90/ >120		60 min.	-15 %	4h

Tab. 9-1 Unfractionated Heparin adjusted to maintain an anti factor Xa level of 0.35 to 0.50 U/ml.

Anti Factor Xa level U/ml?	Hold Next Dose?	Dose Change?	Repeat Anti Factor Xa?
< 0.35	no	increase dose by 25 %	4 h after next dose
0.36 - 0.45	no	increase dose by 15 %	4 h after next dose
0.46 - 0.59	no	increase dose by 10 %	4 h after next dose
0.6 - 1.0	no	no	4 h after next dose
1.1 - 1.25	no	decrease dose by 20 %	4 h after next dose
1.26 - 1.5	no	decrease dose by 30 %	4 h after next dose

Tab. 9-2 Enoxaparin, low molecular weight heparin dosing (Monagle, P, et al.)

Anti Factor Xa level U/ml?	Hold Next Dose?	Dose Change?	Repeat Anti Factor Xa?
1.6 - 2.0	yes for 3h	decrease dose by 40 %	Before next dose then 4h after next dose
> 2.0	yes, until anti factor Xa level is <0.5 U/ml	decrease dose by 50%	Before next dose is administered, if >0.5 U/ml (therapeutic level), do not give next enoxaparin dose & repeat anti Xa level in 12 h. When level <0.5 U/ml, administer 50 % original dose.

Tab. 9-2 Enoxaparin, low molecular weight heparin dosing (Monagle, P, et al.)

Stage	INR	Action
Day 1	1.0 - 1.8	0.2 mg/kg orally
Day 2-4	1.1 - 1.3	repeat day 1 loading dose
	1.4 - 1.9	50 % of day 1 loading dose
	2.0 - 3.0	50 % of day 1 loading dose
	3.1 - 3.5	25 % of day 1 loading dose
	> 3.5	hold dosing until INR is < 3.5

Tab. 9-3 Warfarin loading dose to maintain an INR of 2.7 - 3.5 (Monagle, P, et al.)

Stage	INR	Action
Maintenance : = Day 5 and long term	1.1 - 1.9	increase dose by 40 -50%
	2.0 - 2.4	increase dose by 10 %
	2.7 - 3.5	no change
	3.6 - 4.0	administer next dose at 50 % then restart at 20 % less maintenance dose
	4.1- 5.0	hold one dose then 20 % less maintenance dose

Tab. 9-4 Warfarin Maintenance Dosing for Day 5 and longer to maintain INR 2.7-3.5

INR 2.7 to 3.5	use only warfarin p.o.
INR < 2.7	use warfarin plus enoxaparin as outlined in section 5 until INR ≥ 2.7

Tab. 9-5 Drugs and Dose for specific INR range

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10 Troubleshooting and correcting faults

HOTLINE **Notify Berlin Heart! 866.249.0128**

For themes regarding the Ikus see also the IFU *Stationary Driving Unit Ikus.*

Problem	Cause of problem / action to be taken
Deposits in the pump	Initial deposits: check anticoagulation status and adjust therapy if necessary. If floating deposits are detected (may cause thromboembolic complication): replace the pump, see section 10.1: Replacing the blood pump(s), page 103.
Visible blood pump faults	Replace the pump, see section 10.1: Replacing the blood pump(s), page 103.
Pump membrane remains in the diastolic or systolic position despite vibration / movement of the pump indicating that the Ikus is attempting to provide diastolic or systolic pressure	**Possible causes:** • kinking of the cannula • clotting of the pump • partial malfunction of the Ikus **What to do?** Check for external forces on the cannula and whether it may be necessary to manipulate the cannula. Check for clots in the pump or cannula that may be obstructing flow and replace the pump if necessary, see section 10.1: Replacing the blood pump(s), page 103. Initiate hand-pumping to try to eject the pump, see section 10.2: Driving blood pump(s) with the manual pump, page 107. Switch the patient to the back-up Ikus driving unit.
Pump membrane remains in one position despite the above manipulations	**Additional possible causes:** • High vascular resistance • Defective blood pump There may be air leaking into the space between the first and second layer of the triple-layer pump membrane. This accumulated air may gradually create a “pillowing” effect between the membranes. The top (visible) membrane layer will appear to be continuously in diastole while the bottom two membrane layers are in fact continuously in systole.

Tab. 10-1 Possible problems

Problem	Cause of problem / action to be taken
	As the Ikus continues to provide filling and emptying pressure to the pump, the pump (and possibly the membrane layers) will flex slightly under the changing pressures but will not operate fully. **What to do?** If the patient has high vascular resistance, treat medically as appropriate to reduce the resistance. Adjust system parameters to encourage emptying of the pump. If the pump is defective, replace the pump, see section 10.1: Replacing the blood pump(s), page 103.
Blood is seen in front of or in the area around the stabilization ring in the blood pump.	**Possible causes:** Defect of the blood side layer of the triple layer membrane allows blood to leaking into the space between the layers in the area around the stabilization ring. **What to do?** Replace the pump, see section 10.1: Replacing the blood pump(s), page 103.
Condensation in area around the stabilization ring of the blood pump	Monitor the pump function more frequently for proper blood pump function. Clear fluid content if any in the drive line and air chamber of the pump. Check if the condensate will leave in the next days. Contact Berlin Heart.
Flapping or fluttering of membrane during membrane movement of the pump	**Possible cause:** Partial rupture of one or two layers of the triple-layer membrane. Changes in air pressure during systole and diastole may cause the ruptured layer(s) to flutter. **What to do?** Replace the pump, see section 10.1: Replacing the blood pump(s), page 103.
Blood pump membrane rupture during pump priming (prior to patient support)	**Possible cause:** If the pump membrane is not moved completely to the diastolic position prior to insertion of the de-airing needle, a puncture of the membrane may occur. When the membrane is in the complete diastolic position, the needle will not puncture the membrane. **What to do?** Discard the damaged pump and do not use with the patient. Prime a new pump following the directions in section 5.4: Moving the membrane to the end-of-diastole position, page 52.

Tab. 10-1 Possible problems

Problem	Cause of problem / action to be taken
Cannula rupture	**Possible cause:** Damage to cannula caused by excessive external forces or a sharp object. **What to do?** Immediately stop the support by disconnecting the driving tube from the Ikus. Clamp the cannula. Follow directions to replace the pump, see section 10.1: Replacing the blood pump(s), page 103. After removing the current pump, trim the cannula proximal to the damaged area.
Defective driving tube(s) found through visible or audible inspection of the tube(s) or from Ikus alarm(s)	**Possible causes:** The driving tube has been damaged and the integrity of the tubing may be compromised. There may or may not be an audible sound from air escaping the tubing. This condition may be accompanied by the following error messages. • Pressure error / time error in system 1 (or in system 2 or 3), followed by: • Please connect driving tube **What to do?** If the driving tube is defective, replace it. If a fault in the tubing is not apparent upon inspection, but the Ikus has the above error(s), then follow the directions associated with the error message on the Ikus.
Visible Ikus faults	Notify Berlin Heart.

Tab. 10-1 Possible problems

Problem	Cause of problem / action to be taken
Ikus: the graph display stops moving, parameters cannot be adjusted	**Possible causes** • faulty communications between control computer and laptop • batteries not supplying enough current • the electronics (main and backup control computers) have failed **What to do?** Switch the laptop off and then back on again, wait for the start-up procedure to be completed, then start the monitor program. IMPORTANT: The Ikus continues running with the set parameters. **The graphs remain frozen** The Ikus is operating in emergency pulse mode Notify Berlin Heart. Restart the Ikus after consulting the service department staff.
Acoustic and visual alarm from the Ikus, message **Error: no data from Master** or **Error: no reaction from Master**	**Possible causes** • simultaneous malfunction of both control computers • power supply malfunction **What to do?** Assess the condition of the patient and the hemodynamic values. Notify Berlin Heart immediately.
Pump stands still - no further pump function; acoustic alarm is still audible	**Possible causes** • complete failure of the Ikus • batteries are completely empty or serious fault in the batteries **What to do?** Immediately connect the Ikus to the mains. Until that supply the patient with the manual pump. See also section 10.2: Driving blood pump(s) with the manual pump, page 107. Notify Hotline immediately.

Tab. 10-1 Possible problems

10.1 Replacing the blood pump(s)

WARNING

When replacing a blood pump, follow the instruction given here. Otherwise the duration of the pump stop will be prolonged and the patient might suffer from inadequate support.

The blood pump may only be replaced under sterile conditions!

All effort should be made to minimize the manipulation and distortion of the blood pumps and cannula during the removal of the cable tie(s) to prevent mobilization of deposits.

When connecting the blood pump(s), pay attention to the direction of the arrows on the inflow and outflow stubs! These show the direction of the blood flow.

The cable tie covering the EXCOR cannula on the stub of the blood pump should be removed carefully. Use an appropriate blunt tool. Important: never use a sharp instrument, for example, a scalpel or scissors, to remove the cable tie. This may cause damage to the cannula.

BVAD: If the left pump is being replaced, the right pump must also be stopped while the pump is being replaced. Otherwise there is the risk of pulmonary edema.

NOTICE

If the replacement pump has a larger volume than the one being replaced,
the use of a connector set must be considered
the corresponding parameter in the view *Pump size and single-step mode* must be updated.

MPORTANT: When 2 blood pumps need to be replaced, replace the right blood pump in the first place, subsequently replace the left blood pump.

IMPORTANT: Sedate the patient if necessary and administer a bolus of Heparin according to the anticoagulation protocol.

When using a canula extension set / connecting set: See section 6.3: Cannulae, cannula extension set and connecting set, page 57.

10.1.1 Preparing a replacement blood pump

Material

- 1 replacement blood pump of appropriate type and size
- 1 driving tube, red or blue
- 1 accessory set (for blood pumps with PU valves) with tube connecting set; IMPORTANT: Only the cable ties and cable tie guns provided should be used.

INSTRUCTION

1. Bring membrane to the end-of-diastole position, position de-airing needle, rinse and fill pump with sterile injectable saline (see ssection 5.4: Moving the membrane to the end-of-diastole position, page 52 and section 5.5: De-airing the blood pump, page 52).
2. Connect the driving tube to the respective driving tube connector of the pump.
3. Place the pump, ready for connection, with the titanium connectors pointing upwards.

10.1.2 Replacing the right blood pump (RVAD/ BVAD)

Material

- 1 prepared replacement blood pump (see section 10.1.1: Preparing a replacement blood pump, page 103)
- 1 tube connecting set (cable tie, cable-tie gun), included in the accessory set. Only the cable ties and cable tie guns provided should be used.

Stopping the right blood pump and detaching the blood pump from Ikus

INSTRUCTION

1. Bring the patient into the Trendelenburg position.
2. The cable tie covering the EXCOR cannula on the stub of the blood pump should be removed carefully. Use an appropriate blunt tool.
   Important: never use a sharp instrument, for example, a scalpel or scissors, to remove the cable tie. This may cause damage to the cannula. Check cannulae immediately to make sure they are not damaged.
3. If necessary log into the monitor program by entering user ID and password, confirming the password with **<Enter>**.
4. BVAD: Reduce rate of left blood pump to 30 bpm. Use **<←>**/ **<→>** to navigate cursor to the respective field of the parameter table, then use **<↓>** to adapt value. Confirm with **<Enter>**.
5. In the monitor program, select the option **Pause left** respectively **Pause right** and press **<Enter>** to confirm. Respond to the prompt in the dialog window by pressing the **<X>** key or the **<1>** key. The right blood pump will stop.
   RVAD: **Pause left**
   BVAD: **Pause right**
   The view *Pump size and single-step mode* is displayed.
6. As soon as the right pump has stopped, clamp off the cannulae beneath the right pump to be replaced and slide the cannulae off the pump. If it is necessary to clamp any other part of the cannula that is not covered with velour, cover the part of the cannula that will be clamped with a gauze sponge.
7. Check cannulae for visible deposits. If necessary, remove these deposits carefully.
8. Remove the driving tube of the pump to be replaced from the connector. To do so, take hold of the release sleeve and pull this out of the connector.

Connect new right blood pump to the Ikus

INSTRUCTION

1. Fill the free ends of the cannulae with sterile saline solution. Make sure that all air has been removed. Connect the prepared replacement pump to the cannulae.
2. Plug the new driving tube into the freed connector. The plug snaps into place clearly audible.
3. Check that the plug is securely connected. To do so, grip the plug body above the release sleeve and pull on it. Do not pull from the release sleeve, and never from the tube!
4. Release the tube clamps from the cannulae.

Starting the Ikus

INSTRUCTION

1. Move the cursor to the field **step left** (RVAD) respectively **step right** (BVAD).
2. RVAD: Confirm **Step left** with **<Enter>** to trigger a single step.
   BVAD: Confirm **Step right** with **<Enter>** to trigger a single step.
3. If any air bubbles are visible remove them via the de-airing needle. When all air has been completely removed from the left pump: remove the de-airing needle.
4. Move cursor to the **OK** field and press **<Enter>** to confirm. The driving unit starts up again using the defined parameters.
5. Check whether the pump is filling correctly and, if necessary, adjust the parameters.
6. Secure all connections with cable ties. See section 6.12: Securing the connections, page 76.

10.1.3 Replacing the left blood pump (LVAD/ BVAD)

WARNING

BVAD: If the left pump is being replaced, the right pump must also be stopped while the pump is being replaced. Otherwise there is the risk of pulmonary edema.

Material

- 1 prepared replacement blood pump (see section 10.1.1: Preparing a replacement blood pump, page 103)
- 1 tube connecting set (cable tie, cable-tie gun), included in the accessory set. Only the cable ties and cable tie guns provided should be used.

Stopping the left blood pump and detaching the blood pump from Ikus

INSTRUCTION

1. Bring the patient into the Trendelenburg position.
2. The cable tie covering the EXCOR cannula on the stub of the blood pump should be removed carefully. Use an appropriate blunt tool.
   Important: never use a sharp instrument, for example, a scalpel or scissors, to remove the cable tie. This may cause damage to the cannula. Check cannulae immediately to make sure they are not damaged.

3. If necessary log into the monitor program by entering user ID and password, confirming the password with **<Enter>**.
4. In the monitor program, select the option **Pause left** respectively **Drive pause** and press **<Enter>** to confirm. Respond to the prompt in the dialog window by pressing the **<X>** key or the **<1>** key. The right blood pump will stop.
   LVAD: **Pause left** The view *Pump size and single-step mode* is displayed.
   BVAD: **Drive pause** The view *Select operating mode* is displayed.
5. As soon as the pump(s) has/have stopped, clamp off the cannulae beneath the pump to be replaced and slide the cannulae off the pump. If it is necessary to clamp any other part of the cannula that is not covered with velour, cover the part of the cannula that will be clamped with a gauze sponge.
6. Check cannulae for visible deposits. If necessary, remove these deposits carefully.
7. Remove the driving tube of the left pump to be replaced from the connector. To do so, take hold of the release sleeve and pull this out of the connector.

Connect new left blood pump to the Ikus

INSTRUCTION

1. Fill the free ends of the cannulae with sterile saline solution. Make sure that all air has been removed. Connect the prepared replacement pump to the cannulae.
2. Plug the new driving tube into the freed connector. The plug snaps into place clearly audible.
3. Check that the plug is securely connected. To do so, grip the plug body above the release sleeve and pull on it. Do not pull from the release sleeve, and never from the tube!
4. Release the tube clamps from the cannulae.

Starting the Ikus

INSTRUCTION

1. Move the cursor to the field **step left**.
2. Confirm **Step left** with **<Enter>** to trigger a single step.
3. If any air bubbles are visible remove them via the de-airing needle. When all air has been completely removed from the left pump: remove the de-airing needle.
4. Move cursor to the **OK** field and press **<Enter>** to confirm. The driving unit starts up again using the defined parameters.
5. Check whether the pump is filling correctly and, if necessary, adjust the parameters.
6. Secure all connections with cable ties. See section 6.12: Securing the connections, page 76.

10.2 Driving blood pump(s) with the manual pump

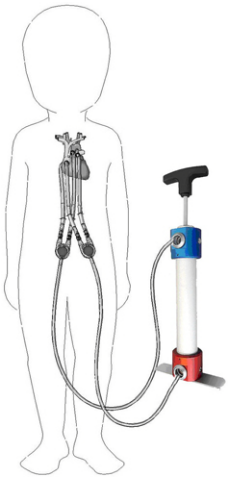


Fig. 10-1 Patient on manual pump

This is necessary if …

- the power supply to the Ikus cannot be ensured
- the Ikus has to be restarted (e.g. emergency operating mode) and there is no replacement Ikus available

WARNING

The use of the manual pump is only permitted for medical personnel trained in the use of it.

Pay attention to the colored markings on the driving tubes and on the connectors of the manual pump. Otherwise, there is a risk of lung edema.

Always keep manual pump attached to the Ikus. Otherwise in an emergency situation the adequate support of the patient is not guaranteed.

Call one or more persons to assist. Otherwise in an emergency situation the adequate support of the patient is not guaranteed.

The driving tubes and cannulae should be arranged in a bend-free position. Otherwise in an emergency situation the adequate support of the patient is not guaranteed.

When operating the manual pump with 1 hand, do not block the valves with your feet (see valve "2" in Fig. 10-2, page 108).

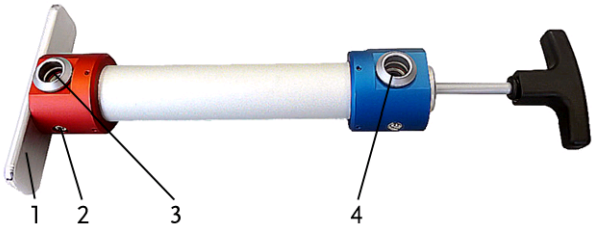
NOTICE

Seal the connector(s) on the Ikus immediately after removing the driving tube(s) in order to avoid contaminates from entering the system.

IMPORTANT: In biventricular mode: the blood pumps are driven asynchronously by the manual pump.

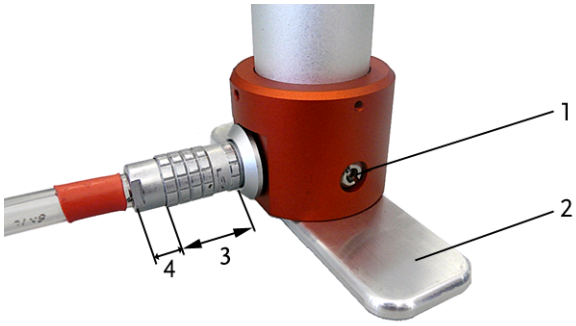
INSTRUCTION

1. The patient is lying down.
2. Disconnect the driving tube(s) from the Ikus. To do so, take hold of the release sleeve and pull this out of the connector.
3. Connect the driving tube(s) to the manual pump. IMPORTANT: Observe the colored markings.
4. Check that the plug is securely connected. To do so, grip the plug body above the release sleeve and pull on it. (see „4“ in Fig. 10-3, page 108) Do not pull from the release sleeve, and never from the tube!
5. Pump steadily and rhythmically at roughly 60 to 80 strokes per minute. Important: Move the piston so far that the membrane reaches its final position. The piston need not necessarily be moved to its end position.
6. Perform a visual check of the blood pump to verify that the membrane is moving and that blood is being pumped.



1 Base plate
2 Valve
3 Connector for driving tube with blue marking
4 Connector for driving tube with blue marking

Fig. 10-2 Manual pump



1 Base
2 Base plate
3 Release sleeve
4 Area above release sleeve

Fig. 10-3 Plug on the driving tube

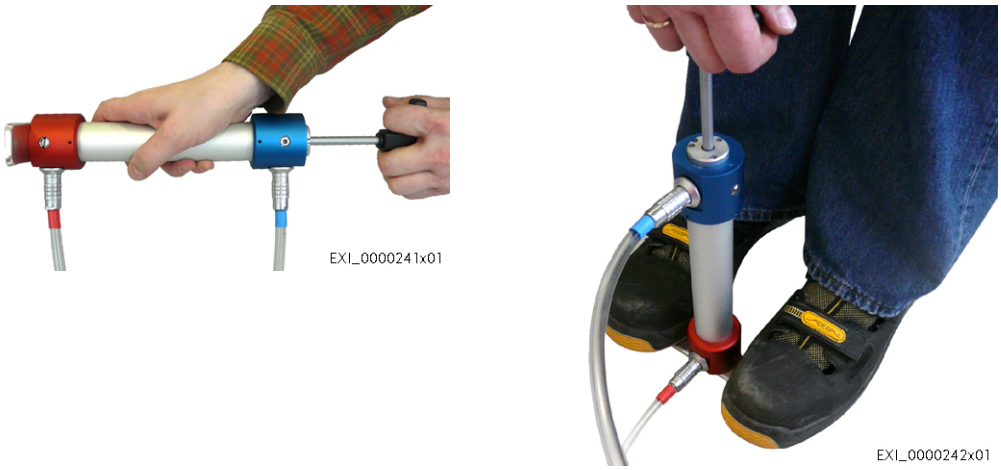


Fig. 10-4 Examples to operate the manual pump

The manual pump can be operated with both hands or with one hand (placing the pump between the feet). Alternating between two-handed or one-handed pumping, as well as using the left or right hand, is allowed. When doing so, care of the patient must remain ensured.

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11 Weaning and Explantation for BTR and BTT

11.1 Weaning Procedure

11.1.1 Introduction

This document summarizes the clinical guideline for weaning and explantation of the EXCOR. The decision to wean the EXCOR should be made cautiously after careful review of all available clinical and laboratory data. This document should be considered a guideline only. As always treatment must be individualized to each patient based on his/her unique clinical circumstances.

It is important to recognize that prolonged pump stoppage and operation of the device at lower beat rates is not recommended due to the risks of blood stagnation and thrombus formation. This risk increases with the smaller blood pumps (e.g. 10, 15, 25 and 30 ml devices) where the luminal sizes and flow rates are the lowest. Therefore, a size-based guideline has been developed to test the adequacy of the native circulation without a prolonged pump stoppage using a combination of gradual weaning, brief pump stoppages, careful anticoagulation monitoring, invasive hemodynamic testing, and a brief afterload challenge. It is not recommended that weaning proceed unless all parameters especially those pertaining to anti-coagulation have been fully optimized. This protocol reflects the most recent understanding of the safest possible weaning strategy based on the collective US and European experience to date. Consultation with *Berlin Heart, Inc.* prior to weaning and explantation is strongly recommended.

11.1.2 Indication

Weaning may be considered in children supported with the EXCOR judged to have sufficient evidence of myocardial recovery to provide adequate systemic perfusion independent of VAD support.

11.1.3 Eligibility Criteria

⚠ WARNING

Continuous reassessment of eligibility criteria is critical to reducing the risks associated with weaning of VAD support. At all times each of the weaning criteria must be satisfied in order to proceed with the weaning protocol.

Special attention must be taken to ensure the patient's anticoagulation status remains within the targeted range.

Weaning of the EXCOR may be considered in subjects who meet the following eligibility criteria:

- LVEDD within normal limits (<98th percentile, or Z-score of +2)
- EF = 45% (i.e. no less than mild dysfunction)
- Lactate <3 mmol/L
- No clinical evidence of thromboembolism or bleeding
- Anticoagulation markers within target parameters

11.1.4 Weaning Protocol

WARNING

Rates < 60 bpm are intended to be used only for implantation and explantation. Never use the *Ikus* with a rate < 60 bpm without constant supervision.

If the patient does not meet the eligibility criteria at any time during the weaning process: Resume pumping at rate prior to any weaning (initial rate, IR).

The weaning protocol can be divided into 5 steps and generally takes one week to complete.

- Day 0 (and throughout the weaning process). Confirmation of eligibility criteria for weaning.
- Day 0. Acute weaning challenge
- Day 1-4. Graduated weaning challenge with non-invasive assessment (echo).
- Day 5. Pump stoppage with invasive hemodynamic assessment with afterload challenge.
- Day 6. Pump stoppage with invasive hemodynamic assessment in OR (full anticoagulation).

This size-based weaning protocol accounts for physiologic differences in heart rate and stroke volume observed in children of varying ages.

11.1.5 10 ml / 15 ml pump

The individual weaning progress is based upon the following parameters:

Parameter	Explanation	Abbr.	Value
initial rate	rate prior to any weaning	IR	Please enter: IR = _____ bpm
weaning rate	lowest rate achieved during weaning process, depends on pump size	WR	50 bpm
total weaning interval	Difference between initial rate and explantation rate: TWI = IR - WR	TWI	Please enter: IR ___ bpm - WR 50 bpm = TWI ___ bpm
reduced rate	rate resumed at the end of day 1 to 3	RR_1 to RR_3	Please refer to Tab. 11-2, page 113.

Tab. 11-1 Important parameters for weaning progress

Reduced rate (RR_x)	Calculation
RR_1	Please enter: RR_1 = WR 50 bpm + 0.75 x TWI (___ bpm) = ____bpm
RR_2	Please enter: RR_2 = WR 50 bpm + 0.50 x TWI (___ bpm) = ____bpm
RR_3	Please enter: RR_3 = WR 50 bpm + 0.25 x TWI (___ bpm) = ____bpm

Tab. 11-2 Reduced rate day 1 to day 3

10 ml / 15 ml pump Weaning Sequence

10 ml / 15 ml pump Weaning Sequence		
Day 0	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance [1]:**	
	1. Administer unfractionated heparin (UFH) 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. 2. After 5 minutes, reduce the pump rate step-wise from IR (_____ bpm) to 30 bpm in increments of 5 bpm q5 min. After 5 minutes at 30 bpm, reassess LV size and function. 3. After an additional 5 minutes (i.e. total time = **10 min** at 30 bpm), stop the pump for **3 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. 4. After 3-minute pump stop, reconnect pump to Ikus and resume pump speed at IR(___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO -STOP** **□ YES - Proceed** **MD_____**

Tab. 11-3 10 ml / 15 ml pump weaning sequence

10 ml / 15 ml pump Weaning Sequence		
Day 1	**After confirmation of eligibility criteria, the following steps should be performed sequentially under echo guidance** [1]:	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. 2. After 5 minutes, reduce the pump rate step-wise by from the IR (_____ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. 3. After a total time of **10 min** at 30 bpm, stop the pump for **3 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. 4. After 3-minute pump stop, reconnect pump to Ikus and resume pumping at rate RR1 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**☐ NO -STOP** **☐ YES - Proceed** **MD_____**
Day 2	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance** [1]:	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. 2. After 5 minutes, reduce the pump rate step-wise from RR1 (_____ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. 3. After a total time of **20 min** at 30 bpm, stop the pump for **3 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. 4. After 3-minute pump stop, reconnect pump to Ikus and resume pumping at RR2 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**☐ NO -STOP** **☐ YES - Proceed** **MD_____**

Tab. 11-3 10 ml / 15 ml pump weaning sequence

10 ml / 15 ml pump Weaning Sequence		
Day 3	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance** [1]:	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. 2. After 5 minutes, reduce the pump rate step-wise from RR2 (___ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. 3. Initiate exercise with gentle age-appropriate play tasks (e.g. rattle, clapping) as clinically appropriate, where possible 4. After a total time of **30 min** at 30 bpm, stop the pump for **3 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected.After 3-minute pump stop, reconnect pump to Ikus and resume pumping at RR3 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO -STOP** **□ YES - Proceed** **MD_____**
Day 4	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance** [1]:	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. 2. After 5 minutes, reduce pump rate step-wise from RR3 (___ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. 3. Initiate exercise with gentle age-appropriate play tasks (e.g. rattle, clapping) as clinically appropriate, where possible. 4. After a total time of **30 min** at 30 bpm, stop the pump for **3 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. 5. After a 3-minute pump stop: If the patient meets all eligibility criteria, reconnect pump to Ikus and resume pumping at WR (50 bpm). If the patient does not meet all criteria, reconnect Ikus and resume pumping at IR.	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO -STOP** **□ YES - Proceed** **MD_____**

Tab. 11-3 10 ml / 15 ml pump weaning sequence

10 ml / 15 ml pump Weaning Sequence		
Day 5	**After confirmation of eligibility criteria, the following steps should be performed in the cath lab under echo guidance** [1]: 1. Obtain standard access for RHC (if possible with out sedation). 2. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. 3. After 5 minutes, reduce the pump rate step-wise from WR (50 bpm) to 30 bpm in increments of 5 bpm q5 min. After 5 minutes at 30 bpm, reassess LV size and function. 4. After a total time of **10 min** at 30 bpm, stop the pump for **3 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. 5. After 3 minutes, initiate norepinephrine infusion at 0.01 mcg/kg/min IV gtt titrated to MAP 20% above baseline x 5 min. While doing so, proceed pumping manually twice q30 seconds. 6. If LV size and function acceptable, proceed pumping manually twice q30 seconds for **3 min**. While doing so, reassess LV size & function, and record RAP, PAP, PCWP and MVS. 7. After 6-minute pump stop: If the patient meets all eligibility criteria, reconnect pump to Ikus and resume pumping at 50 bpm until the actual surgical procedure of explantation takes place. If the patient does not meet all criteria, reconnect Ikus and resume pumping at IR.	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO -STOP** **□ YES - Proceed** **MD_____**

Tab. 11-3 10 ml / 15 ml pump weaning sequence

[1] TEE unless echo windows insufficient. The last weaning increment may be less than 5 bpm if the wean interval is not a multiple of 5.

11.1.6 25 / 30 ml pump

The individual weaning progress is based upon the following parameters:

Parameter	Explanation	Abbr.	Value
initial rate	rate prior to any weaning	IR	Please enter:
weaning rate	lowest rate achieved during weaning process, depends on pump size	WR	40 bpm

Tab. 11-4 Important parameters for weaning progress

Parameter	Explanation	Abbr.	Value
total weaning interval	Difference between initial rate and explantation rate: TWI = IR - WR	TWI	Please enter: IR ___ bpm - WR 40 bpm = TWI ___ bpm
reduced rate	rate resumed at the end of day 1 to 3	RR_1 to RR_3	Please refer Tab. 11-5, page 117.

Tab. 11-4 Important parameters for weaning progress

Reduced rate (RR_x)	Calculation
RR_1	Please enter: RR_1 = WR 40 bpm + 0.75 x TWI (___ bpm) = ____bpm
RR_2	Please enter: RR_2 = WR 40 bpm + 0.50 x TWI (___ bpm) = ____bpm
RR_3	Please enter: RR_3 = WR 40 bpm + 0.25 x TWI (___ bpm) = ____bpm

Tab. 11-5 Reduced rate day 1 to day 3

25 / 30 ml pump Weaning Sequence

25 / 30 ml pump Weaning Sequence		
Day 0	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer unfractionated heparin (UFH) 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise from IR (_____ bpm) to 30 bpm in increments of 5 bpm q5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** After an additional 5 minutes (i.e. total time = 10 min at 30 bpm), stop the pump for 5 min and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **4.** After 5-minute pump stop, reconnect pump to Ikus and resume pump speed at IR(___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	☐ **NO - STOP** ☐ **YES - Proceed** **MD_____**

Tab. 11-6 25 / 30 ml pump Weaning Sequence

25 / 30 ml pump Weaning Sequence		
Day 1	**After confirmation of eligibility criteria, the following steps should be performed sequentially under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise by from the IR (_____ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** After a total time of **10 min** at 30 bpm, stop the pump for **5 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **4.** After 5-minute pump stop, reconnect pump to Ikus and resume pumping at rate RR1 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO - STOP** **□ YES - Proceed** **MD_____**
Day 2	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise from RR1 (_____ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** After a total time of **20 min** at 30 bpm, stop the pump for **10 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **4.** After 10-minute pump stop, reconnect pump to Ikus and resume pumping at RR2 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO - STOP** **□ YES - Proceed** **MD_____**

Tab. 11-6 25 / 30 ml pump Weaning Sequence

25 / 30 ml pump Weaning Sequence		
Day 3	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise from RR2 (___ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** Initiate exercise with gentle age-appropriate play tasks (e.g. patty cake) as clinically appropriate, where possible **4.** After a total time of **30 min** at 30 bpm, stop the pump for **10 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **5.** After 10-minute pump stop, reconnect pump to Ikus and resume pumping at RR3 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	□ **NO - STOP** □ **YES - Proceed** **MD_____**
Day 4	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce pump rate step-wise from RR_3 (___ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** Initiate exercise with gentle age-appropriate play tasks (e.g. patty cake) as clinically appropriate, where possible. **4.** After a total time of **30 min** at 30 bpm, stop the pump for **15 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **5.** After a 15-minute pump stop: If the patient meets all eligibility criteria, reconnect pump to Ikus and resume pumping at WR (40 bpm). If the patient does not meet all criteria, reconnect Ikus and resume pumping at IR.	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	□ **NO - STOP** □ **YES - Proceed** **MD_____**

Tab. 11-6 25 / 30 ml pump Weaning Sequence

25 / 30 ml pump Weaning Sequence		
Day 5	**After confirmation of eligibility criteria, the following steps should be performed in the cath lab under echo guidance:**[1] **1.** Obtain standard access for RHC (if possible with out sedation). **2.** Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **3.** After 5 minutes, reduce the pump rate step-wise from WR (50 bpm) to 30 bpm in increments of 5 bpm q5 min. After 5 minutes at 30 bpm, reassess LV size and function. **4.** After a total time of **30 min** at 30 bpm, stop the pump for **15 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **5.** After 15 minutes, initiate norepinephrine infusion at 0.01 mcg/kg/min IV gtt titrated to MAP 20% above baseline x 5 min. While doing so, proceed pumping manually twice q30 seconds. **6.** If LV size and function acceptable, proceed pumping manually twice q30 seconds for **5 min**. While doing so, reassess LV size & function, and record RAP, PAP, PCWP and MVS. **7.** After 20-minute pump stop: If the patient meets all eligibility criteria, reconnect pump to Ikus and resume pumping at 50 bpm until the actual surgical procedure of explantation takes place. If the patient does not meet all criteria, reconnect Ikus and resume pumping at IR.	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO - STOP** **□ YES - Proceed** **MD_____**

Tab. 11-6 25 / 30 ml pump Weaning Sequence

[1] TEE unless echo windows insufficient. The last weaning increment may be less than 5 bpm if the wean interval is not a multiple of 5.

11.1.7 50 / 60 ml pump

The individual weaning progress is based upon the following parameters:

Parameter	Explanation	Abbr.	Value
initial rate	rate prior to any weaning	IR	Please enter: IR = _____ bpm
weaning rate	lowest rate achieved during weaning process, depends on pump size	WR	30 bpm

Tab. 11-7 Important parameters for weaning progress

Parameter	Explanation	Abbr.	Value
total weaning interval	Difference between initial rate and explantation rate: TWI = IR - WR	TWI	Please enter: IR ___ bpm - WR 30 bpm = TWI ___ bpm
reduced rate	rate resumed at the end of day 1 to 3	RR_1 to RR_3	Please refer to Tab. 11-8, page 121.

Tab. 11-7 Important parameters for weaning progress

Reduced rate (RR_x)	Calculation
RR_1	Please enter: RR_1 = WR 30 bpm + 0.75 x TWI (___ bpm) = ____bpm
RR_2	Please enter: RR_2 = WR 30 bpm + 0.50 x TWI (___ bpm) = ____bpm
RR_3	Please enter: RR_3 = WR 30 bpm + 0.25 x TWI (___ bpm) = ____bpm

Tab. 11-8 Reduced rate day 1 to day 3

50 / 60 ml pump Weaning Sequence

50 / 60 ml pump Weaning Sequence		
Day 0	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer unfractionated heparin (UFH) 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise from IR (_____ bpm) to 30 bpm in increments of 5 bpm q5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** After an additional 5 minutes (i.e. total time = 10 min at 30 bpm), stop the pump for 5 min and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **4.** After 5-minute pump stop, reconnect pump to Ikus and resume pump speed at IR(___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	☐ **NO - STOP** ☐ **YES - Proceed** **MD_____**

Tab. 11-9 50 / 60 ml pump Weaning Sequence

50 / 60 ml pump Weaning Sequence		
Day 1	**After confirmation of eligibility criteria, the following steps should be performed sequentially under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise by from the IR (_____ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** After a total time of **10 min** at 30 bpm, stop the pump for **10 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **4.** After 10-minute pump stop, reconnect pump to Ikus and resume pumping at rate RR1 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO - STOP** **□ YES - Proceed** **MD_____**
Day 2	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise from RR1 (_____ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** After a total time of **15 min** at 30 bpm, stop the pump for **15 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **4.** After 15-minute pump stop, reconnect pump to Ikus and resume pumping at RR2 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO - STOP** **□ YES - Proceed** **MD_____**

Tab. 11-9 50 / 60 ml pump Weaning Sequence

50 / 60 ml pump Weaning Sequence		
Day 3	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce the pump rate step-wise from RR2 (___ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** Initiate exercise with gentle age-appropriate play tasks (e.g. ambulate) as clinically appropriate, where possible **4.** After a total time of **30 min** at 30 bpm, stop the pump for **20 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **5.** After 20-minute pump stop, reconnect pump to Ikus and resume pumping at RR3 (___ bpm).	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO - STOP** **□ YES - Proceed** **MD_____**
Day 4	**After confirmation of eligibility criteria, the following steps should be performed under echo guidance:**[1]	
	1. Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **2.** After 5 minutes, reduce pump rate step-wise from RR_3 (___ bpm) to 30 bpm in increments of 5 bpm q 5 min. After 5 minutes at 30 bpm, reassess LV size and function. **3.** Initiate exercise with gentle age-appropriate play tasks (e.g. ambulate) as clinically appropriate, where possible. **4.** After a total time of **30 min** at 30 bpm, stop the pump for **30 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **5.** After a 15-minute pump stop: If the patient meets all eligibility criteria, reconnect pump to Ikus and resume pumping at WR (40 bpm). If the patient does not meet all criteria, reconnect Ikus and resume pumping at IR.	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	**□ NO - STOP** **□ YES - Proceed** **MD_____**

Tab. 11-9 50 / 60 ml pump Weaning Sequence

50 / 60 ml pump Weaning Sequence		
Day 5	**After confirmation of eligibility criteria, the following steps should be performed in the cath lab under echo guidance**[1] **1.** Obtain standard access for RHC (if possible with out sedation). **2.** Administer UFH 75 units/kg x _____ kg = _____ mg IV x 1 [max 5000 units]. **3.** Assess LV size and function to obtain data for comparison. **4.** Stop the pump for **15 min** and reassess LV size and function. During pump stoppage, use the manual pump to pump twice q30 seconds to minimize the risk of thrombus formation due to blood stagnation while Ikus is disconnected. **5.** After 15 minutes, initiate norepinephrine infusion at 0.01 mcg/kg/min IV gtt titrated to MAP 20% above baseline x 5 min. While doing so, proceed pumping manually twice q30 seconds. **6.** If LV size and function acceptable, proceed pumping manually twice q30 seconds for **15 min**. While doing so, reassess LV size & function, and record RAP, PAP, PCWP and MVS. **7.** After 30-minute pump stop: If the patient meets all eligibility criteria, reconnect pump to Ikus and resume pumping at 50 bpm until the actual surgical procedure of explantation takes place. If the patient does not meet all criteria, reconnect Ikus and resume pumping at IR.	
	Did the patient satisfy all 5 eligibility criteria throughout the period of weaning and pump stoppage?	☐ **NO - STOP** ☐ **YES - Proceed** **MD_____**

Tab. 11-9 50 / 60 ml pump Weaning Sequence

[1] TEE unless echo windows insufficient. The last weaning increment may be less than 5 bpm if the wean interval is not a multiple of 5.

11.1.8 Explantation Criteria

NOTICE

ASA and dipyridamole should be discontinued 24-hours prior to device explantation; coumadin/Enoxaparin should be transitioned back to unfractionated heparin (titrated to therapeutic levels).

Milrinone 0.75 µg/kg/min should be started 12 hours prior explantation. ACE inhibitor, ß-Blocker and Spirinolactone should be not stopped.

In the operating room, explantation should be considered if the following criteria are met with the pump stopped for 20 minutes (after anticoagulation has been established in the target range for cardiopulmonary bypass):

- LVEDD less than 98th percentile (Z-score less than +2)
- EF ≥ 45% (i.e. no more than mild ventricular dysfunction)
- Normotensive on only Milrinone (no other inotropes)
- Lactate <3 mmol/L
- LVEDP < 12 mmHg
- Resting CI of > 2.8 L/min/m2

Surgery should be performed without Cardiopulmonary Bypass. Control all bleeding immediately during and post implantation.

11.2 Explantation for BTR

11.2.1 Explantation with univentricular support

The procedure is analogous to that used after BTT (see section 11.3: Explantation for BTT, page 126). Sew over all anastomosis areas where cannulae were placed.

11.2.2 Explantation after biventricular support

Stopping the right pump

INSTRUCTION

1. Select **Pause right** (see Fig. 11-1, page 125), then press **<Enter>** to confirm. Respond to the prompt in the dialog window by pressing the **<X>** key or the **<1>** key. The right pump will stop. The view Pump size and single-step mode is shown (see IFU). The cursor is located on the **OK** field.
2. Unplug the driving tube of the right pump from the connector on the Ikus. Use the seal plug to seal the connector.
3. To confirm the **OK** selection, press **<Enter>**. The Ikus continues running. The screen shows the standard view.

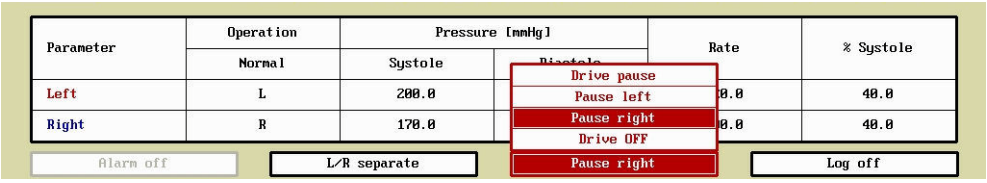

Fig. 11-1 Pause right

Switching the Ikus off

WARNING

The Ikus power switch (toggle switch) should always be in the *[I]* position, even if the main switch (key switch) is in the *[0]* position!. Otherwise there is a risk that the drive may fail in future due to the Ikus batteries being totally discharged.

Always follow the above sequence of operations. Always use the key switch to switch off the Ikus.

Do not switch the Ikus off unless the batteries are fully charged. Leave the Ikus switched on until all yellow LEDs light up, then switch off the Ikus with main switch (key switch).

Keep all driving tube connectors covered at all times when not in use.

INSTRUCTION

1. Put the patient on cardiopulmonary bypass (CPB).
2. Disconnect the driving tubes and connect both tank units to the Ikus.
3. Leave the Ikus running with the tank units until the patient is stable on CPB and the blood pumps have been explanted.
4. Next in the monitor program, select the option **Drive OFF** (see Fig. 11-2, page 127) and press **<Enter>** to confirm.
5. Respond to the prompt in the dialog window by pressing the **<X>** key or the **<1>** key. The system stops operation immediately and writes an operating log.
6. Disconnect the driving tube(s) from the connector(s). To do so, take hold of the plug's release sleeve and pull the plug out of the connector.
7. Use the seal plugs to seal the driving tube connector sockets.
8. Wait until the log has been completed. When the message **Switch drive off with main switch!** appears, press **<F10>** to shut down the monitor program. Confirm by pressing the **<X>** key or the **<1>** key.
9. Select **3. End** (**<3>**, see Fig. 11-3, page 127) in the start menu and switch off the laptop.
10. Switch the Ikus off, provided that the batteries are fully charged. To do so, turn the key switch to *[0]* position.

11.3 Explantation for BTT

NOTICE

When planning and timing the transplantation, be aware that massive adhesions may exist in the transplant recipient.

Preparing the donor organ

ADVICE

Leave adequate lengths of the aorta and the pulmonary artery attached to the donor organ in order to be able to continue using those parts of the original vessels used for anastomosis of the VAD cannulae.

Leave the Ikus running with the tank units until the patient is stable on CPB and the blood pumps have been explanted.

Switching the Ikus off

WARNING

The Ikus power switch (toggle switch) should always be in the [I] position, even if the main switch (key switch) is in the [0] position! Otherwise there is a risk that the drive may fail due to the Ikus batteries being totally discharged.

CAUTION

Always follow the above sequence of operations. Always use the key switch to switch off the Ikus.

Do not switch the Ikus off unless the batteries are fully charged. To do this leave the Ikus switched on until all yellow LEDs light up, then switch the Ikus off using the key switch.

INSTRUCTION

1. Put the patient on cardiopulmonary bypass.
2. Disconnect the driving tubes and connect both tank units to the Ikus.
3. Leave the Ikus running with the tank units until the patient is stable on CPB and the blood pumps have been explanted.
4. Next in the monitor program, select the Drive OFF option and press <Enter> to confirm (see Fig. 11-2, page 127).
5. Respond to the prompt in the dialog window by pressing the <X> key or the <1> key. The system stops operation immediately and writes an operating log.
6. Disconnect the driving tube(s) from the connector(s). To do so, take hold of the release sleeve and pull this out of the connector.
7. Use the seal plugs to seal the driving tube connectors.
8. Wait until the log has been completed. When the message Switch drive off with main switch! appears, press <F10> to shut down the monitor program. Confirm by pressing the <X> key or the <1> key.
9. Select 3. End (<3>, see Fig. 11-3, page 127) in the start menu and switch off the laptop.
10. Switch the Ikus off, provided that the batteries are fully charged. To do so, turn the key switch to [0] position.

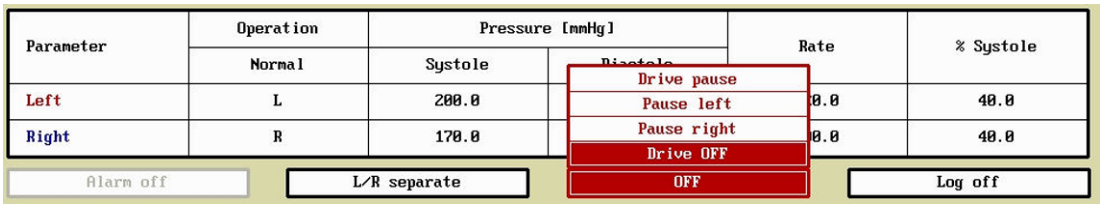

Fig. 11-2 Drive OFF

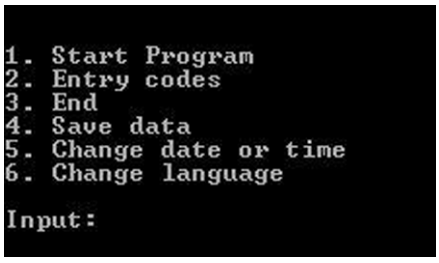

Fig. 11-3 Start menu

Removing the VAD cannulae

INSTRUCTION

1. Clamp off the cannulae.
2. Disconnect the pump from the cannulae.
3. Remove the cannulae. Sew over the anastomosis areas of the atrium.

The remaining procedure is the same as for any primary orthotopic heart transplantation.

12 Appendix

12.1 Overview: Product range and possible combinations

12.1.1 Blood pumps

Article number	Volume [ml]	∅ Inflow / outflow [mm]
P10P-001	10	6
P15P-001	15	9
P25P-001x01	25	9
P30P-001x01	30	9
P50P-001	50	12
P60P-001	60	12

Tab. 12-1 Blood pumps PU valves

12.1.2 Overview: Relationship: body weight – pump size

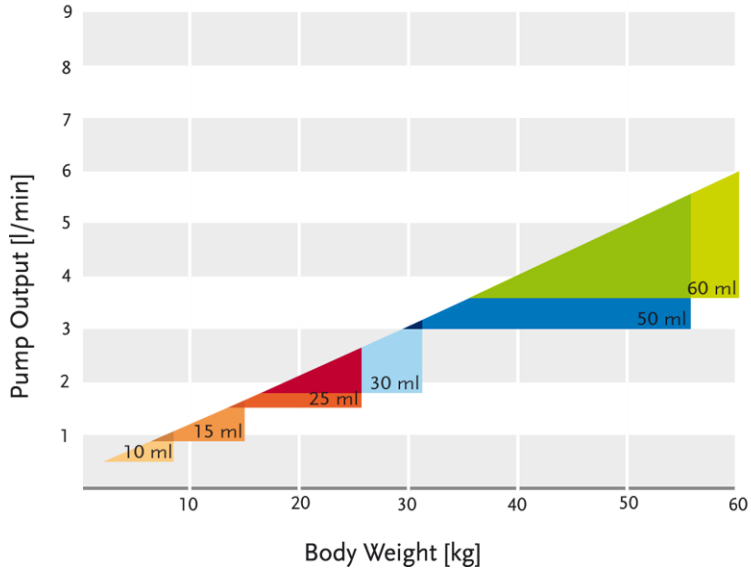

Fig. 12-1 Relationship: body weight - pump size

The final decision of pump selection should be made by the implanting physician based on the individual patients needs and the weight/pump output guidance represented in this graph. Note that the graph represents common clinical use and not the maximum technical performance of the blood pumps.

12.1.3 LV apex cannulae

Article number	∅ Lumen [mm]	Overall length [mm]	Length of head [mm]	Angle of head [°]
C14A-040	5	220	14	0
C18A-020	6	250	18	0
C22A-004	12/9[1]	270/220[1]	28	0
C27A-001	12	265	38	0
[1] with/ without stage cut off				

Tab. 12-2 LV apex cannulae

12.1.4 Atrial cannulae

Article number	∅ Lumen [mm]	Length of corpus [mm]	Length of head [mm]	Angle of head [°]
C15V-040	5	200	15	80
C19V-020	6	250	19	80
C22V-004	9/12[1]	280/240[1]	22	45
C25V-004	9/12[1]	280/240[1]	25	45
C22V-002	12	330	22	45
C26V-002	12	330	26	45
[1] with/ without stage cut off				

Tab. 12-3 Atrial cannulae

12.1.5 Arterial cannulae

Article number	∅ [mm]	Overall length [mm]	Length of head [mm]	Angle of head [°]	Remarks
C80G-040	5	200	4,5	80	
C80G-021	6	250	5	80	
C60G-004	12/9[1]	280/240[1]	0	60	with flexible reinforcement
C85G-004	12/9[1]	280/240[1]	0	85	with flexible reinforcement

Tab. 12-4 Arterial cannulae

Article number	∅ [mm]	Overall length [mm]	Length of head [mm]	Angle of head [°]	Remarks
C60G-002	12	330	0	60	with flexible reinforcement
C85G-002	12	330	0	85	with flexible reinforcement
[1] with/ without stage cut off					

Tab. 12-4 Arterial cannulae

12.1.6 Overview: Which cannulae should be used for which pump?

Which pump?	Pump connector Ø [mm]	Cannula lumen Ø [mm] where cannula joins pump	Which inflow cannula?	Which outflow cannula?
P10-001	6	5 5 6 6	C15V-040 (AT) C14A-040 (AP) C19V-020 (AT) C18A-020 (AP)	C80G-040 C80G-021
P15P-001	9	6 6 9 9 9	C19V-020 (AT;CS) C18A-020 (AP;CS) C22V-004 (AT;SC) C25V-004 (AT;SC) C22A-004 (AP;SC)	C80G-021 (CS) C60G-004 C85G-004
P25P-001x01 P30P-001x01	9	6 6 9 9 9	C19V-020 (AT;CS) C18A-020 (AP;CS) C22V-004 (AT;SC) C25V-004 (AT;SC) C22A-004 (AP;SC)	C80G-021 (CS) C60G-004 C85G-004 (SC)
P50P-001 P60P-001	12	12 12 12 12 12 12	C22V-004 (AT;SO) C25V-004 (AT;SO) C22V-002 (AT) C26V-002 (AT) C22A-004 (AP; SO) C27A-001 (AP)	C60G-004 (SO;CS) C85G-004 (SO;CS) C60G-002 C85G-002
Explanation:	AT: atrial cannula AP: apex cannula SO: staged (stepped diameter) cannula, original diameter SC: staged (stepped diameter) cannula, diameter after cutting to size CS: connecting set required (A06-009 or A09-012 accordingly)			

Tab. 12-5 Which cannula for which pump?

12.1.7 System accessories

Article number	Designation
T00L-001	Accessory set for blood pumps with PU valves (membrane set, de-airing set and tube connecting set)accessory set:for blood pumps with PU valves
L20H-002	Driving tube, red; length: 200 cm
L20H-003	Driving tube, blue; length: 200 cm

Tab. 12-6 System Accessories

12.1.8 Driving unit

Article number	Designation
D03I-111	EXCOR® Stationary Driving Unit Ikus (115V/ 60Hz) - SW 3.41

Tab. 12-7 Driving unit

12.1.9 Special components

Article number	Designation
A06-006	Cannula extension set, ∅ 6/6 mm
A09-009	Cannula extension set, ∅ 9/9 mm
A12-012	Cannula extension set, ∅ 12/12 mm
A06-009	Connecting set for cannulae, ∅ 6/9 mm
A09-012	Connecting set for cannulae, ∅ 9/12 mm

Tab. 12-8 Connecting set and cannula extension set

12.1.10 Maximum rates for the pump-cannula combinations

Cannulation		Blood pumps					
Ø inflow cannula	**Ø outflow cannula**	**10 ml**	**15 ml**	**25 ml**	**30 ml**	**50 ml**	**60 ml**
5 mm	**5 mm**	130 bpm					
6 mm	**5 mm**	130 bpm	130 bpm				
6 mm	**6 mm**	130 bpm	130 bpm	80 bpm	65 bpm		
9 mm	**6 mm**		130 bpm	100 bpm	90 bpm		
9 mm	**9 mm**		130 bpm	130 bpm	130 bpm	130 bpm	105 bpm
12 mm	**9 mm**					130 bpm	105 bpm
12 mm	**12 mm**					130 bpm	125 bpm

Tab. 12-9 Maximum rates for the pump-cannula combinations

Pump-cannula combinations in which not every parameter combination is recommended (pump rate, % systole, systolic and diastolic pressure) can lead to incomplete filling and emptying of the blood pump.

rate value (bpm)

The value indicated is the upper threshold for pump rates. Values that are below the upper threshold are within the acceptable range. Values that are higher than the upper threshold are in a questionable range.

The threshold values have been determinated (in vitro) taking a mean arterial blood pressure of 120 mmHg as a basis.

rate value (bpm)

Red marked values displayed on the laptop: These parameter combination (pump rate, % systole, systolic and diastolic pressure) for these pump-cannula combination can lead to incomplete filling and emptying of the blood pump(s). Observe the filling behavior of the blood pump(s)!

in biventricular mode

The lower value of both pump rates (corresponding to the pump sizes used) must also be considered. The higher of the 2 pump rates should be disregarded.

12.1.11 Blood pump combinations in biventricular mode

left blood pump	right blood pump
10 ml	10 ml
15 ml	15 ml
30 ml	25 ml
60 ml	50 ml

Tab. 12-10 Recommended combinations

Check whether a blood pump combination that is not recommended has been selected for the patient. The final decision on the combination of blood pumps and cannulae is to be reached by the implanting surgeon, in consultation with Berlin Heart, Inc Clinical Affairs.

12.1.12 Relative systolic duration

The relative systolic duration is adjustable in the range of 20% and 70%. The upper and lower threshold (20-30% and 60-70%) are marked in red on the laptop. For these values it cannot be guaranteed that the activated pressure parameters are achievable for each single case.

12.2 Technical specifications

Electro-pneumatic extracorporeal ventricular assist device **EXCOR® Pediatric VAD with Stationary Driving Unit Ikus**	
Manufactured by:	Berlin Heart GmbH Wiesenweg 10 2247 Berlin Germany
Classification	Class 3
Overall system (except sterile products)	
Ambient temperature in operation	+10 °C bis +30 °C; with restrictions of the battery performance up to +35°C
Ambient temperature, transportation and storage	-10 °C bis +50 °C ; 6 h warming-up period before commissioning after transportation
Max. permitted ambient magnetic field strength	10 A/m

Tab. 12-11 Technical specifications

Electro-pneumatic extracorporeal ventricular assist device EXCOR® Pediatric VAD with Stationary Driving Unit Ikus	
Relative humidity of environment	45 to 75 %
Ambient atmospheric pressure	max. 2000 m (6562 ft) above MSL (mean sea level)
Pump	
Dimensions	Refer to product data sheets
Material	Casing and membranes: polyurethane Driving tube adapter: polyoxymethylene Connectors: titanium
Coating of blood contact surfaces	Carmeda® BioActive Surface (CBAS®)
Max. period of use	max. 1 year
Cannulae	
Dimensions	Refer to product data sheets
Material	Silicone, partially reinforced with plastic webbing, partially encased with suture-suitable polyester velour; some equipped with flexible metal reinforcement: wire 2 mm, circular steel Rd 1.4301; apex cannula with a titanium alloy shell
For all sterile products	
Long-term storage conditions	Temperature: +15°C to 25°C Relative humidity: 35 % to 50 % Store in a dry place!
Ikus	
Dimensions (W x H x D)	46 x 95 x 73 cm with laptop cover down (approx. 18.5 x 37.5 x 29 inches) 46 x 120 x 73 cm with laptop cover open (approx. 18.5 x 47.5 x 29 inches)
Weight	100.6 kg (approx. 219 lb)
Input voltage	AC 115 V
Frequency	60 Hz

Tab. 12-11 Technical specifications

Electro-pneumatic extracorporeal ventricular assist device **EXCOR® Pediatric VAD with Stationary Driving Unit Ikus**	
Power drawn	575 VA
Mains fuse	5 A
Mains cable	10 A, hospital grade
Connector External alarm	electrical data: max 1 A, 24 V insulation specifications: 2.5 mm/ 4 mm clearance and creepage distance between alarm contact and 24 V extra low voltage inside the device (coil-sided) insulation test voltage: 500 V
Protection class	IPX1 (protection against touching live parts not tested, tested safety from vertically dripping water)
Pump rate	30 to 150 bpm
Sound level of acoustic alarm	71 dB (A)
Systolic pressure:	60 to 350 mmHg
Diastolic pressure	-100 to 0 mmHg
Pressure display accuracy	±10%
Relative systolic duration	20 % to 70%
Off-mains operating time	max. 30 minutes
Battery charging time	6 h
Maintenance interval	2000 operating hours (at the latest after 6 months). In the event of permanently higher ambient temperatures than recommended, the maintenance intervals can shorten drastically.
Product life Ikus	max. 8 years

Tab. 12-11 Technical specifications

12.3 Symbols and tags

	Refer to instruction booklet / manual		Example of symbol for NumLk and Caps Lock status LED on laptop
	Caution		Type B applied part
	General warning sign		Type CF applied part
	Catalogue number		MR unsafe (Magnetic Resonance Imaging unsafe)
	Batch code		Keep dry
	Serial number		WEEE symbol: not to be disposed of with consumer waste
	Manufacturer		Can be disposed of with consumer waste
	Date of manufacture		Use-by date
	Sterilized using ethylene oxide		Do not use if package is damaged
	Do not re-use		Do not resterilize
	Humidity limitation		Temperature limit

Fig. 12-2 Symbols used on labeling

12.4 Sample copy: Ikus Incoming Checklist

IKUS INCOMING CHECKLIST

Berlin Heart®

Always refer to the Instructions for Use of EXCOR Pediatric VAD!

Ikus LOT#: (located under red drive tube connection port) ..... – ..... Name of clinical site: .....

Please ensure that the checklist below has been satisfactorily completed:

	checked
Ikus driver and replacement driver are available	☐
Remove Ikus drivers from crates and inspect for damage and/or broken parts	☐
Manual pump included (located and secured under laptop)	☐
Locate and inspect for the following accessories (either loose or in white box):	
⇨ Mains power supply cable ☐	⇨ Keys ☐
⇨ Envelope with default password ☐	⇨ Connector Plug for External Alarm ☐

⚠ If the driver is damaged or there are missing parts:
Do not use the driver. Notify Berlin Heart Clinical Affairs (866) 249 - 0128

Ikus driver initial start-up:

Caution!
- Keep the driving tube connectors covered at all times when not in use.
- The Ikus mains power switch (rocker switch) should always be in the ON/ EIN position – even when Ikus is in battery mode or is switched off (i.e. not in operation).

	checked
Connect the Ikus to the mains power (emergency outlet). Secure the mains cable with the plug clip on the Ikus driver. Ensure that the mains power switch (rocker switch) is set to ON/ EIN.	☐
Turn the key switch to the ON [I] position. The battery charge indicator (LED lights) will light up and the number of hours the driving unit has been operated to date will be displayed. The mains power indicator lights up.	☐
Switch on the laptop. The language selection menu appears. Select the desired language by pressing the corresponding number key. You do not have to press <Enter> to confirm this selection.	☐
The start menu is displayed on the laptop. Select the "Start program" option (<1>). Enter your user number and password. Confirm the password with <Enter>. Ikus will carry out a self-test. Wait for the test phase to be concluded (this takes several minutes). Do not acknowledge the acoustic signal. The messages in the message window will inform you of the status of the test. If Ikus is found to be operating correctly, the "Operating mode" view will be displayed next.	☐
Check that the batteries are adequately charged (full bar of LED lights).	☐
Shut down the monitoring program as instructed in the dialog window.	☐
When instructed in the message window, use the key switch to switch off Ikus. Important: The mains power switch (rocker switch) remains set to ON/ EIN.	☐

⚠ If the Ikus has detected a fault during start-up or the self test:

An error message will appear in the message window. Switch the Ikus off, wait for at least 10 minutes, and begin the start procedure again as described above. If the error message persists, notify Berlin Heart Clinical Affairs: (866) 249 - 0128

Remarks:

..... Name ..... Signature ..... Date

Please complete and fax this form back to Berlin Heart, Inc. Fax No: (877) 237 - 5464

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12.5 Implantation record form

Berlin Heart®

IMPLANTATION RECORD FORM

EXCOR® VAD Ped

This form applies **only** to USA and Canada

Please fill out the form (5 pages), and fax it to Berlin Heart, Inc. *immediately* after implantation (fax: 866.540.5026)
After replacing a blood pump, please fill out the "Pump Replacement" section (page 2), list the supplies used on page 3-5, and fax (5 pages) to Berlin Heart Inc. (fax: 866.540.5026)

PATIENT INFORMATION

Hospital			City/Country	
Patient's initials:	**Sex** m ☐ f ☐	**Age:**	**Height** [cm]	**Weight** [kg]
Patient-No.: (BH Site No. followed by the patient No. ie: 004-103)	**Indication** Ischemic CMP ☐	Idiopathic CMP ☐	Acute Myocarditis ☐	
	Postcardiotomy ☐	Acute Myocardial Infarction ☐		
	Congenital ☐	.....	Other ☐	

PRE- IMPLANTATION CONDITION

Urgency of implantation elective ☐ urgent ☐ emergency ☐

INTERMACS level

1 ☐ Critical cardiogenic shock despite escalating support
2 ☐ Progressive decline with inotropic dependence
3 ☐ Clinically stable with mild to moderate inotropic dependence
4 ☐ Recurrent, no refractory, advanced heart failure that can be stabilized with intervention
5 ☐ Exertion intolerant but is comfortable at rest and able to perform activities of daily living with slight difficulty
6 ☐ Exertion limited; is able to perform mild activity, but fatigue results within a few minutes of any meaningful physical exertion
7 ☐ Advanced NYHA functional class III

On ventilator	no ☐	yes ☐	since ..... (days)	
Other MCS	no ☐	yes ☐		
		IABP ☐	since ..... (date)	
		ECMO ☐	since ..... (date)	
Another VAD support	no ☐	yes ☐	since ..... (date)	
On transplantation list	no ☐	yes ☐	since ..... (date)	
CPR within 24h	no ☐	yes ☐	unknown ☐	
Dialysis/Hemofiltration within 72h	no ☐	yes ☐	unknown ☐	
History of stroke	no ☐	yes ☐	unknown ☐	
History of prev. thor. surg.	no ☐	yes ☐	unknown ☐	

PRE- IMPLANTATION HEMODYNAMICS (most recent – if any parameter is not available please mark: n.a.)

MAP [mmHg]	**CVP** [mmHg]	**PAP mean** [mmHg]	**LVEDP** [mmHg]	**LVEF %** **FS %**
Cardiac output [l/min]	**Cardiac Index** [l/min/sqm]	**LVEDD** [mm]		

IMPLANTATION DETAILS

Implantation date [mm/dd/yy]	**Surgeon** [name]	**Type** BVAD ☐ LVAD ☐ RVAD ☐	**Left-sided cannulation** apical ☐ atrial ☐	**Pump type** Tilting-disk valve ☐ PU valve ☐

LVAD pump size:	10 ml ☐	15 ml ☐	25 ml ☐	30 ml ☐	50 ml ☐	60 ml ☐	80 ml ☐
RVAD pump size:	10 ml ☐	15 ml ☐	25 ml ☐	30 ml ☐	50 ml ☐	60 ml ☐	80 ml ☐

Berlin Heart, Inc ., 200 Valleywood Road, Suite B100
The Woodlands, TX 77380
www.berlinheart.com

1000068x08

Berlin Heart®

☐ **Pump replacement**

Left pump ☐	Reason for replacement .....
Date:	Location of deposit inflow valve ☐ outflow valve ☐ pump chamber ☐
Right pump ☐	Reason for replacement .....
Date:	Location of deposit inflow valve ☐ outflow valve ☐ pump chamber ☐

☐ **Device Explant**

Date:	HTx ☐ weaned ☐ died ☐ primary cause: ..... Remarks: ....

Berlin Heart®

Please record the lot numbers of the used EXCOR® components and indicate the availability of replacement components and fax all to Berlin Heart, Inc. *immediately* after implantation (fax: 866.540.5026).

Hospital/City ..... **Date of Implantation** .....

Patient ID (BH Site No. followed by the patient No. ie: 004-103) .....

Ikus-No. ..... **Ikus hours of operation** .....

Replacement Ikus available ? yes ☐ no ☐ **Replacement Ikus hours of operation**

Replacement Ikus-No. ....

Item	Article No.	Lot-No. LVAD used	RVAD used	Replacement available ? yes	no
EXCOR Blood Pumps with PU valves					
10 ml in/out Ø 6 mm	P10P-001			☐	☐
15 ml in/out Ø 9 mm	P15P-001			☐	☐
25 ml in/out Ø 9 mm	P25P-001x01			☐	☐
30 ml in/out Ø 9 mm	P30P-001x01			☐	☐
50 ml in/out Ø 12 mm	P50P-001			☐	☐
60 ml in/out Ø 12 mm	P60P-001			☐	☐
80 ml in/out Ø 12 mm	P80P-001***			☐	☐
EXCOR Blood Pumps with Tilting-disk valves					
50 ml in/out Ø 12 mm	P50M-001***			☐	☐
60 ml in/out Ø 12 mm	P60M-001***			☐	☐
80 ml in/out Ø 12 mm	P80M-001***			☐	☐
80 ml **out/in** Ø 12 mm (in/out exchanged)	P80M-005***			☐	☐
80 ml in/out Ø 16 mm	P80M-003***			☐	☐
80 ml **out/in** Ø 16 mm (in/out exchanged)	P80M-004***			☐	☐

*** Not available for general use in the US or Canada
+++ Not available for general use in the US

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www.berlinheart.com

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Item	Article No.	Lot-No. LVAD used	RVAD used	Replacement available ? yes	no
EXCOR Apex Cannulae					
Ø 5 mm, L 22 cm (Apex cannula for infants)	C14A-040			☐	☐
Ø 6 mm, L 25 cm (Apex cannula for small children)	C18A-020			☐	☐
Ø 12/9 mm, L 27 cm (Apex pediatric cannula, staged)	C22A-004			☐	☐
Ø 12 mm, L 26,5 cm (Apex cannula, one-piece)	C27A-001			☐	☐
Ø 16 mm, L 33 cm (Apex cannula)	C41A-050***			☐	☐
EXCOR Atrial Cannulae					
Ø 5 mm, L 20 cm, head 15 mm (Atrial cannula for infants)	C15V-040			☐	☐
Ø 6 mm, L 25 cm, head 19 mm (Atrial cannula, small children)	C19V-020			☐	☐
Ø 12/9 mm, L 28 cm, head 22 mm (Atrial ped. cannula, stag.)	C22V-004			☐	☐
Ø 12/9 mm, L 28 cm, head 25 mm (Atrial ped. cannula, stag.)	C25V-004			☐	☐
Ø 12 mm, L 33 cm, head 22 mm (Atrial cannula)	C22V-002			☐	☐
Ø 12 mm, L 33 cm, head 26 mm (Atrial cannula)	C26V-002			☐	☐
EXCOR Arterial Cannulae					
Ø 5 mm, L 20 cm (Arterial cannula for infants)	C80G-040			☐	☐
Ø 6 mm, L 25 cm (Arterial cannula for small children)	C80G-021			☐	☐
Ø 12/9 mm, L 26 cm (Graft-adapter ped. cannula, staged)	C00P-004+++			☐	☐
Ø 12/9 mm, L 28 cm, 85° (Arterial ped. cannula, staged)	C85G-004			☐	☐
Ø 12/9 mm, L 28 cm, 60° (Arterial ped. cannula, staged)	C60G-004			☐	☐
Ø 12 mm, L 33 cm, 60° (Arterial cannula)	C60G-002			☐	☐
Ø 12 mm, L 33 cm, 85° (Arterial cannula)	C85G-002			☐	☐
Ø 12 mm, L 26 cm (Graft-adapter cannula)	C00P-001+++			☐	☐
Ø 16/12 mm, L 36 cm, 85° (Arterial cannula, staged)	C85G-050+++			☐	☐
Ø 16 mm, L 26 cm (Graft-adapter cannula)	C00P-050+++			☐	☐

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Item	Article No.	Lot-No. LVAD used	RVAD used	Replacement available ? yes	no
Connecting Set for Cannulae					
Ø 6/9 mm	A06-009			☐	☐
Ø 9/12 mm	A09-012			☐	☐
Ø 12/16 mm	A12-016***			☐	☐
Cannula Extension Set					
Ø 6/6 mm	A06-006			☐	☐
Ø 9/9 mm	A09-009			☐	☐
Ø 12/12 mm	A12-012			☐	☐
Accessories					
Accessory set Tilting-disk valves	T00L-001***			☐	☐
Accessory set PU-valves	T00L-002			☐	☐
Driving tube, red Ø 6/8 mm, L 2 m	L20H-002			☐	☐
Driving tube, blue Ø 6/8 mm, L 2 m	L20H-003			☐	☐
Tank unit	1600422			☐	☐

*** Not available for general use in the US or Canada
+++ Not available for general use in the US

Date _____	**Signature** _____
Name _____	**Contact Phone No.** _____

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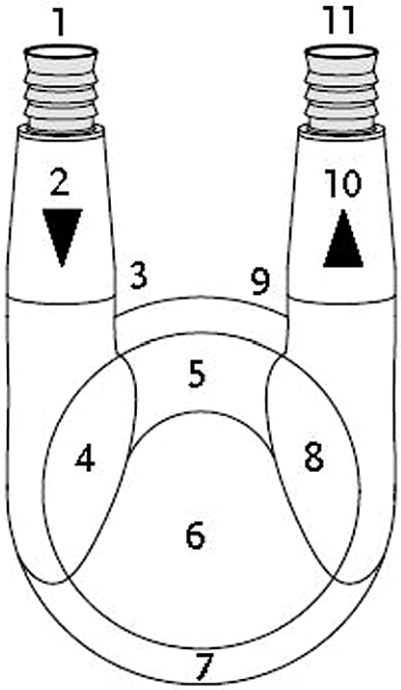
The Woodlands, TX 77380
www.berlinheart.com

12.6 Sample copy: EXCOR pump log



1 transition inflow cannula – inflow connector
2 inflow stub in front of inflow valve
3 inflow valve
4 inflow stub behind inflow valve
5 area between inflow and outflow stubs
6 remaining area of blood chamber
7 transition blood chamber - membrane (directly above the reinforcement ring)
8 outflow stub in front of outflow valve
9 transition outflow connector – outflow cannula
10 outflow valve
11 outflow stub behind outflow valve

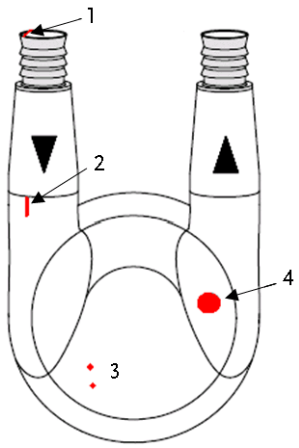
Fig. 12-3 EXCOR blood pump with checkpoint numbers

ADVICE To briefly describe the findings, use the following letter codes:

p	small punctual deposit	f	small strand
P	large punctual deposit	F	large strand
a	small area of deposit	t	small thrombus
A	large area of deposit	T	large thrombus
~ above the respective letter indicates floating deposits			

Tab. 12-12 Notation for letter code

Example: Plotting of the deposits



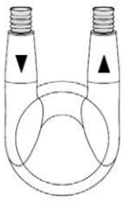
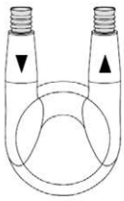
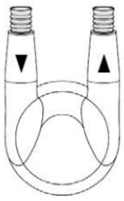
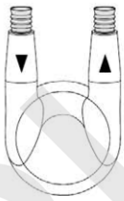
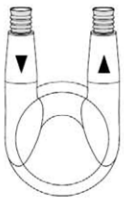
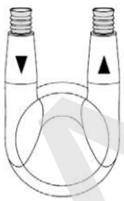
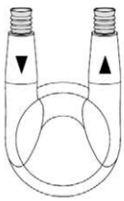
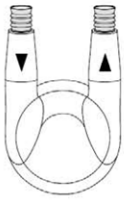
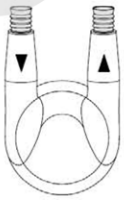
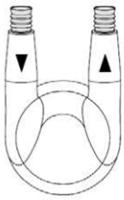
1 small laminar deposit
2 small suture on the inflow valve
3 small specks
4 larger laminar deposit

Fig. 12-4 Plotting of the deposits

Example: Notation with letter code

			Linke Pumpe/ Left pump	ml: 50ml				No.: 0815						
Datum date	Zeit time	Name Sign.		1	2	3	4	5	6	7	8	9	10	11
01.01.	8:00	z.B.		a		F			p		A			

Fig. 12-5 Example: Notation with letter code

			Linke Pumpe/ Left pump	ml:				No.:							Rechte Pumpe/ Right pump	ml:				No.:						
Datum date	Zeit time	Name Sign.		1	2	3	4	5	6	7	8	9	10	11		1	2	3	4	5	6	8	7	9	10	11
																										
																										
Datum date	Zeit time	Name Sign.		1	2	3	4	5	6	7	8	9	10	11		1	2	3	4	5	6	8	7	9	10	11
																										
Datum date	Zeit time	Name Sign.		1	2	3	4	5	6	7	8	9	10	11		1	2	3	4	5	6	8	7	9	10	11
																										

12.7 Pump performance flow sheet

Berlin Heart
Berlin Heart, Inc.

Berlin Heart EXCOR®
Pump Performance Flow Sheet
(FM-CA-031, Rev. 1)

Ikus-№ ___ - _____

Date	Time	MODE	RATE		Drive Pressures				% Systole		Membrane Movement				
		I=Internal S=Sync A=Async SP=Separate	L	R	LEFT (mmHg)		RIGHT (mmHg)		L	R	LEFT		RIGHT	
			bpm	bpm	systole	diastole	systole	diastole	%	%	eject	fill	eject	fill
Sample:	9:15 AM	S	60	60	210	-30	130	-30	40	40	+ +	+ –	+ +	+ +

Membrane movement:
+ + complete or almost complete (max. 1 small wrinkle in membrane) movement of membrane to end position
+ - incomplete ejection or filling movement (membrane has more than 1 small wrinkle at end position of ejection or filling movement)
- - bad ejection or filling (membrane moves only partially or not at all

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