



# A Novel Strategy for the Mechanical Subpulmonary Support in Failing Fontan Patients

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## Abstract

**Background** The number of single ventricle patients undergoing Fontan palliation and surviving to adulthood worldwide has steadily increased in recent years. Nevertheless, the Fontan circulation is destined to fail. Ultimately, heart transplantation (HTx) remains the definitive treatment option. Due a shortage of organs, mechanical circulatory support in the form of ventricular assist devices (VADs) is widely used to bridge heart failure patients to HTx, but these devices have been mainly developed to address the needs of normal anatomies. A novel venous cannula has been developed as part of the EXCOR® VAD to provide subpulmonary support in these patients. Its clinical application is investigated in the “Registry to Assess the Safety and Feasibility of the Subpulmonary Support with the Novel Venous Cannula in Patients with Failing/Absence of the Right Heart” (RegiVe study, NCT04782232).

**Methods** RegiVe is a multicenter, international, observational, prospective, non-randomized registry aiming to collect the routine clinical data of up to 20 patients. The primary endpoints address device performance and safety, while the secondary endpoints target organ status and overall safety (according to the Interagency Registry for Mechanically Assisted Circulatory Support – INTERMACS – definitions). Data analysis will be performed by means of descriptive statistics.

**Results** RegiVe has received the favorable opinion of an independent ethics committee and enrollment has recently started.

**Conclusion** RegiVe is the first study evaluating the use of a medical device specifically developed for subpulmonary support of failing Fontan patients. The study will provide important insight and further information on this cohort and help to improve a dedicated VAD strategy.

## Keywords

- ▶ circulatory assist devices
- ▶ congenital heart disease
- ▶ transplantation
- ▶ heart

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## Introduction

The cardiac single ventricle (SV) population is steadily increasing due to recent advances in medical therapy and clinical management.<sup>1</sup> The lack of a subpulmonary ventricle is palliated surgically by means of a series of operations aiming to establish the separation of the pulmonary and systemic circulations. However, the full reconstruction of a circulation with two functional ventricles is not feasible in these patients, and the absence of a subpulmonary chamber remains the pivotal characteristic of Fontan physiology, being the factor that impacts post-palliation outcomes the most.<sup>2</sup> In this setting, the burden of the entire circulation is taken on by the only available ventricle, which in turn relies on low pulmonary vascular resistance and is accompanied by systemic venous hypertension.<sup>2</sup> Therefore, the Fontan circulation has a limited lifespan and will inevitably fail even in patients who have been apparently stable for years. Recent data estimated a long-term survival of over 80% at 20 years post-Fontan completion.<sup>3</sup> However, SV patients will eventually develop heart failure (HF) and have several long-term comorbidities, culminating in early death.<sup>3</sup> In these patients, HF presents with distinct phenotypes depending on the mechanism of failure.<sup>1</sup> Fontan failure or the failing Fontan is characterized by typical cardiac failure (pump failure) that includes cardiac morbidities (such as systolic or diastolic dysfunction, atrioventricular valve regurgitation, thromboembolism in the Fontan circulation, and arrhythmias) or circulatory failure caused by extracardiac morbidities—i.e., Fontan circulation failure—such as lymphatic disorders and end-organ dysfunction.<sup>1,2,4</sup> As such, it is noteworthy to distinguish pathologies due to classical HF—such as dyspnea, weakness, edema, or organ dysfunction caused by hypoperfusion—from the specific disorders due to the failure of the subpulmonary circulation presenting with considerable effects on the venous and lymphatic systems resulting in protein-losing enteropathy (PLE), plastic bronchitis (PB), and Fontan-associated liver disease (FALD) with or without ascites.

Heart transplantation (HTx) represents the only definitive option when failure occurs. SV patients are among the most high-risk cohort of congenital heart disease (CHD) patients for HTx and the optimal timing of transplantation is controversial.<sup>1,5</sup> Nevertheless, when patients survive the early post-HTx period, the long-term outcomes are similar to biventricular CHD patients.<sup>6</sup> As a consequence, a common consensus is developing that recognizes the feasibility of HTx in this cohort given appropriate prior considerations, such as candidate selection, patient monitoring while listed, and surgical and clinical management.<sup>7</sup>

In this setting, the use of mechanical circulatory support (MCS) is at the center of the scientific debate. A clear benefit may be predicted in terms of patient stabilization on the waiting list by means of protection of the end-organs and preconditioning to improve post-HTx outcomes.<sup>8</sup> MCS devices are generally considered inadequate for failing Fontan patients as they have been developed to address pump failure through ventricular support and decompression in regular

anatomies.<sup>9,10</sup> When speaking about MCS in Fontan patients, it is necessary to distinguish between systemic and subpulmonary support, as failure may occur with preserved systemic ventricular function. In these cases, systemic support alone is not sufficient.<sup>11</sup>

Targeted devices addressing the specific challenges, anatomies, and hemodynamics of failing Fontan patients are currently lacking.<sup>9,10</sup> Two adult cases of isolated subpulmonary support with a ventricular assist device (VAD) have been reported.<sup>12,13</sup> In both cases, an EXCOR® VAD (Berlin Heart GmbH, Germany) was connected to the pulmonary circulation by an artificial reservoir mimicking the right atrium. Other reports have described the use of an EXCOR® VAD in a biventricular VAD (BVAD) setting leading to successful HTx.<sup>14,15</sup> These experiences constituted the first proof-of-concept of the efficacy of subpulmonary support in improving the clinical condition of patients with Fontan failure and the feasibility of a bridge-to-transplantation approach.

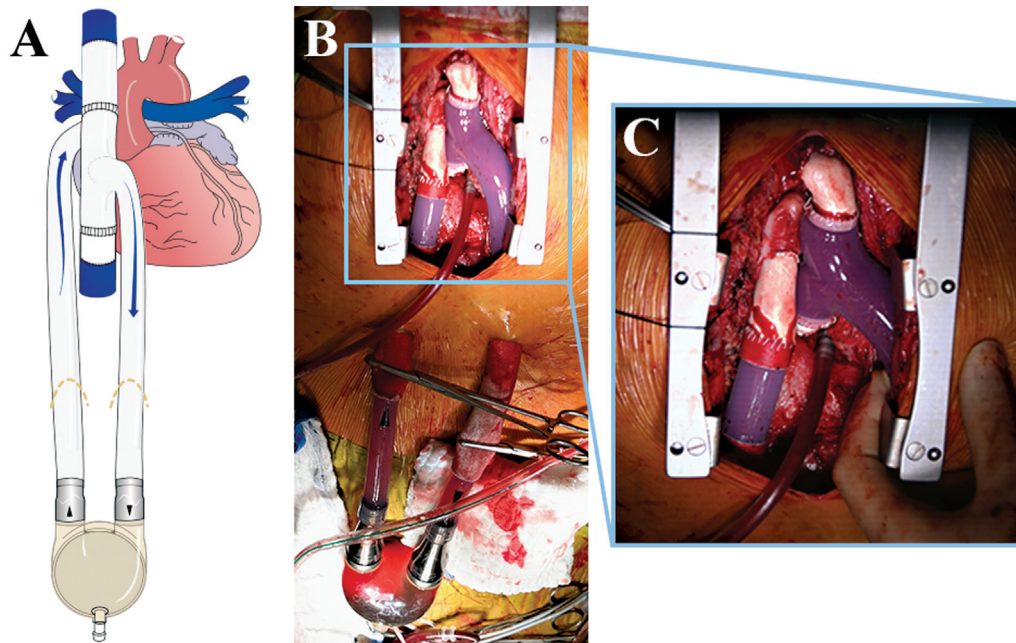
To this end, a novel venous cannula (VC) has been developed as an additional component of the EXCOR® VAD (—Fig. 1A). The VC received the CE mark in 2020 and was designed to address the clinical demand for a subpulmonary MCS device. The clinical application of the VC is being investigated in the “Registry to Assess the Safety and Feasibility of the Subpulmonary Support with the Novel Venous Cannula in Patients with Failing/Absence of the Right Heart” (RegiVe study).

## Patients and Methods

### Study Design and Patient Population

The RegiVe study is a multicenter, international, observational, prospective, non-randomized registry to collect routine clinical data of up to 20 patients. The study is designed in alignment with the principles and guidance of the Good Clinical Practice (GCP). The study population consists of children and adults with venous connection abnormalities in need of a VAD and in whom a functional right heart is missing. This definition includes SV patients of different etiologies that have been surgically palliated and for whom the Fontan circulation is failing due to the absence of subpulmonary support. The indication for VC implantation must comply with the manufacturer’s instructions-for-use (IfU). A failing Fontan patient is eligible for enrollment in the registry if (1) the EXCOR® VAD indications as an isolated right heart support (right VAD) or BVAD apply, (2) the patient is listed or at least eligible for HTx, and (3) the patient’s body surface area is greater than or equal to 1.2 m<sup>2</sup>. Patients with any of the contraindications to EXCOR® VAD therapy listed in the IfU are excluded from participation in the study. Patients included in the study will receive the EXCOR® VAD as part of their regular treatment and medical care as defined by their treating physician.

The study is planned to last 42 months overall, with a follow-up period of up to 12 months while each subject is on VAD support. Any outcome event (i.e., transplantation, weaning, death) qualifies the patient for ending their participation in the study.



**Fig. 1** The venous cannula consists of a body made from silicone and suture rings for anastomosis to the vascular grafts connecting the superior and inferior vena cavae, and it is intended for single ventricle patients with failing Fontan palliation. (A) EXCOR® Revive approach illustrating the use of the EXCOR® VAD with the venous cannula as isolated subpulmonary support. (B, C) Venous cannula in situ. (images B and C are provided by courtesy of Bernd H. Schnitzer, Berlin Heart GmbH, and have been taken at the Ludwig Maximilian University of Munich on the occasion of the first case<sup>16</sup>).

### Study Objectives and Endpoints

This prospective registry lies in the regulatory framework of post-market clinical investigations. The study objective is to monitor the VC in terms of device safety and performance while in use according to the IfU. Special attention is paid to the well-being and quality of life (QoL) of the treated patients and the feasibility of subpulmonary support. To this end, the study evaluates the clinical course of the patient over a time period that allows for short- and long-term assessments. In addition, the study aims to confirm the benefit-risk ratio as well as to detect emerging risks, if any.

Accordingly, primary endpoints have been defined to address the performance and safety of the VC in the context of EXCOR® VAD therapy based on the 30-day rates of mortality, of major bleeding, and of device thrombus (short-term) and survival to HTx (long-term). The secondary endpoints move the focus to the effect of therapy on Fontan-associated complications and safety. Improvement of hemodynamics is assessed in the 30 days post-implantation (short-term) using specific parameters such as central venous pressure, central venous saturation, lactate, blood pressure, and urine production, all with respect to the patient's baseline. The improvement of function in at least one organ with dysfunction (e.g., kidneys, liver) is evaluated in the 12 months post-implantation (long term), again with respect to the patient's baseline. Additionally, recovery from typical failing Fontan symptoms such as PLE, PB, or FALD will be assessed. The safety endpoint considers the rate of all adverse events in the 12 months post-implantation.

### Study Visits

The RegiVe study includes a total of eight visits, spanning from pre-implantation status to a 1-year follow-up (►Table 1). The pre-implantation visit (V – 1) screens eligibility criteria and collects demographic and baseline data on the enrolled subjects. The day of VC and EXCOR® VAD implantation corresponds to V0 and is used to gather information regarding the procedure and the device. The implantation date marks the beginning of safety data collection. Three visits are planned shortly after surgery at 1 day (V1), 1 week (V2), and 1 month (V3), and together define the short-term time points of the study. Three further study visits span the follow-up period at 3 months (V4), 6 months (V5), and 12 months (V6) post-implantation.

### Data Management

As per the nature of a noninvasive observational study, all data will be gathered according to the specific clinical and medical routines of the study sites. Data collection will be performed by means of an online-based electronic case report form. The selected electronic data capture system is certified for compliance with the FDA CFR 21 Part 11 regulation and ISO 14155:2020 (GCP) guideline.

### Collected Data

Basic demographic data regarding the patient's age, gender, and height will be collected at the screening visit (before implantation). The patient's medical history will be recorded to gather information about the SV etiology, palliation, previous operations with sternotomy and interventions,

**Table 1** Visit schedule of the RegiVe study

	V – 1	V0	V1	V2	V3	V4	V5	V6
	Baseline/screening	Implantation	1-d FU	1-wk FU	1-mo FU	3-mo FU	6-mo FU	1-y FU
Written informed consent	x							
Inclusion/exclusion criteria	x							
Demographics	x							
Medical history	x							
Clinical condition	x				x		x	x
Echocardiography	x		x	x	x	x	x	x
Cardiac catheterization	x							
ICU catheterization	x		x	x	x	(x) <sup>a</sup>	(x) <sup>a</sup>	(x) <sup>a</sup>
Secondary organ dysfunction	x			x	x	x	x	x
Device implantation		x						
Quality of life	(x) <sup>b</sup>			(x) <sup>b</sup>	(x) <sup>b</sup>	x	x	
Relevant concomitant medication	x	x	x	x	x	x	x	x
Safety and outcome assessment		x	x	x	x	x	x	x

Abbreviations: ICU, intensive care unit; FU, follow-up, V, visit.

Note: The study comprises eight time points of data capture spanning from baseline to 1 year post-procedural follow-up.

<sup>a</sup>Assessments that will be performed only if applicable.

<sup>b</sup>Potential baseline for the evaluation of quality of life upon patient's condition.

presence of implanted pacemakers or cardioverter defibrillators, previous and current Fontan-associated complications, and other comorbidities. Thoracic images will be collected to aid implantation by means of 3D fitting simulations.

The evaluation of the patient's clinical condition will entail the collection of general information regarding systolic and diastolic blood pressure, heart rate, oxygen saturation at rest, weight, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and New York Heart Association (NYHA) class, and HTx listing.

Echocardiography will also be performed to evaluate ventricular function, valve regurgitation, and ventricular ejection. The assessment of hemodynamics will be performed by means of standard cardiac catheterization performed in the intensive care unit and/or in the catheterization laboratory, as applicable. Central venous pressure and central venous oxygen saturation will be collected to evaluate hemodynamics. Further catheterization parameters will also be collected if available.

The assessment of secondary organ function includes a wide set of parameters collected by means of both qualitative and quantitative analyses. The study aims to monitor the complex, and often interconnected, status of Fontan-associated complications. To this end, laboratory analyses will be performed to evaluate the status of the liver, kidneys, lymphatic system, and cardiovascular system (►Table 2). To

evaluate hepatic morphology, imaging will be performed by means of liver ultrasound (to verify the presence of splenomegaly, heterogenous liver parenchyma, segmental atrophy/hypertrophy, surface nodularity, hepatic vein dilatation, abnormal hepatic vein architecture, hyperechoic lesions, ascites) and transient elastography. Liver status will also be evaluated by means of the Model for End-Stage Liver Disease eXcluding INR (MELD-XI) score and Varices, Ascites, Splenomegaly, Thrombocytopenia Varices, Ascites, Splenomegaly, Thrombocytopenia (VAST) scores.

Information about the existence of other common failing Fontan-associated complications such as arrhythmias, PLE, PB, occurrence of thromboembolic events, pleural effusions, lung congestion, and peripheral edema will be collected qualitatively.

One of the major objectives of treatment is improving the patient's QoL. The study will assess QoL using the HF-specific "Cardiac Module" of the established Pediatric Quality of Life Inventory (PedsQL). The questionnaire enables the collection of age-adjusted data from four age groups: (1) children (8–12 years old), (2) adolescents (13–18 years old), (3) young adults from 18 to 25 years old, and (4) adults older than 25 years. The PedsQL baseline will be set according to the patient's physical and mental condition at one of three different visits: V – 1 (pre-implantation V2 (1-week follow-up), or V3 (1-month follow-up). The follow-up will be evaluated at V4 (3-month follow-up) and V5 (6-month follow-up).

**Table 2** Laboratory parameters by target organ

Target	Parameters
Liver	Direct and total bilirubin
	Liver enzymes (aspartate aminotransferase, alanine aminotransferase, $\gamma$ -glutamyl transferase)
	Albumin
	Platelet count
Kidneys	Creatinine
	Blood urea nitrogen
	Albumin-to-creatinine ratio
	Estimated glomerular filtration rate
Lymphatic system	Albumin
	Total protein
	Leukocyte count
Cardiovascular system	N-terminal pro-B-type natriuretic peptide
	Lactate
Infection status	Procalcitonin
	C-reactive protein
	Leukocyte count

Note: The study captures laboratory data for appropriate assessment of end-organ function and medical condition.

The study will capture data about relevant concomitant medications. Special attention will be paid to anticoagulation management, HF management (i.e., diuretics and inotropes), and albumin supplement. Specific blood values will be collected to monitor anticoagulation therapy, such as partial thromboplastin time and anti-factor Xa levels for heparin, arachidonic acid activity for aspirin, international normalized ratio for vitamin K antagonists, and adenosine diphosphate activity for clopidogrel and dipyridamole.

Information will be collected regarding the surgical procedure, such as the cardiopulmonary bypass time and the type of cannulation. Data on EXCOR® VAD implantation will be gathered, including VAD configuration, cannula types, pump type, and the driving unit used, together with its settings. Additional information about the EXCOR® VAD system will be further collected during the study in case components require replacement for any reason.

Starting from V0, all adverse events and device deficiencies will be collected and assessed for seriousness, severity, and relationship with the investigational procedure, investigational device, and other EXCOR® VAD components. Adverse device effects will be further categorized according to the INTERMACS definitions.

### Statistical Analysis

Due to the nature of an observational registry study, statistical analyses will be performed descriptively and will include 95% confidence intervals. Continuous variables will be summarized by reporting the number of observations, mean,

standard deviation, median, minimum, and maximum. Categorical variables will be displayed using frequency tables showing the number and percentage of participants within a particular category. For long-term assessments, Kaplan–Meier statistics will be estimated for endpoints with available event data. Missing values will not be imputed.

### Ethical Considerations

All study activities at a specific site will start only after a favorable opinion is given by an independent ethics committee. Participation is voluntary and each patient and/or his/her parents reserve the right to withdraw his/her consent at any time during the study without any disadvantage.

### Results

The study protocol was finalized on November 10<sup>th</sup>, 2020, and registered on ClinicalTrials.gov with the identifier “NCT04782232”. A favorable opinion was given by the International Medical and Dental Ethics Commission (IMDEC) on November 30<sup>th</sup>, 2020. In addition, each study center will apply for a favorable opinion from their responsible local ethics committee. The first patient receiving the VC worldwide was enrolled in the study in early 2021 (► Fig. 1B, C).<sup>16</sup>

### Discussion

The RegiVe study investigates the impact of subpulmonary VAD support as a bridge to HTx in palliated SV children and adults suffering from failure of the Fontan circulation. This population constitutes a rare cohort of CHD patients that, so far, has been orphaned by the advances of the MCS field. Recently, the VC has been developed to specifically address this unmet clinical need for patients indicated for EXCOR® VAD therapy. The VC aims to satisfy two requirements of key clinical relevance: (1) improving the patient’s hemodynamics and end-organ function, thus increasing the chances of patient survival, and reducing morbidities while on the HTx list, and (2) easing and accelerating the surgery by enabling a standardized implantation technique. The device is available in three sizes to facilitate patient fitting and can be connected to all EXCOR® VAD driving units (► Table 3). VAD support is provided by the EXCOR® VAD in a subpulmonary position alone or in a BVAD configuration as part of a broader approach named “EXCOR® Revive.”

EXCOR® Revive puts the focus on the preservation or re-establishment of appropriate end-organ status. This can be seen as the addition of a new meaning to the general MCS paradigm of heart support alone. Indeed, the goals of end-organ recovery and hemodynamic improvement can be achievable only if the classic target of isolated SV unloading is enriched by the introduction of cavopulmonary support. Even with preserved ventricular function, a considerable number of extracardiac comorbidities arise as a consequence of the chronically elevated central venous pressure and venous congestion, leading to organ damage and remodeling processes.<sup>1,2,4</sup> Although both cardiac and noncardiac manifestations of Fontan failure constitute indications for HTx,

**Table 3** Available sizes of the venous cannula

Article number	Pump connector inner diameter [mm]	Inner diameter SVC [mm]	Inner diameter IVC [mm]	Distance SVC-IVC [mm]
C1418F-002m	12 (50-, 60-, and 80-mL blood pumps)	14	18	49
C1620F-002m		16	20	
C1822F-002m		18	22	

Abbreviations: IVC, inferior vena cava; SVC, superior vena cava.

Note: The venous cannula is available in three different sizes for allowing the optimal fitting to different patient's anatomies.

they may also severely jeopardize patient survival while on the transplant list and negatively affect post-HTx outcomes.<sup>5,17</sup>

Thus, there is a demand for effective preconditioning of patients prior to HTx. Applying EXCOR® VAD therapy with the VC would constitute a modern cornerstone of treatment tailored to improve failing Fontan physiology. Consequently, this study pays great attention to the evaluation of failing Fontan manifestations by means of qualitative and quantitative assessments of the heart, lymphatic system, and end organs. Considering that Fontan failure is determined by different mechanisms and occurs in different modalities, the patient's condition while on device support will be appraised using a multidimensional approach based on groups of variables that are clustered by organ and system. In particular, for surveillance of the targeted organ/system, specific laboratory values and imaging findings are selected according to the testing toolkit for Fontan patients proposed by the American Heart Association.<sup>1</sup> Following this suggestion, the assessment will receive supportive information from appropriate evaluation of cardiac function.

Some of the most relevant comorbidities of the failing Fontan circulation are PLE and PB. Both are abnormalities of the lymphatic system driven by the increased central venous pressure and venous congestion.<sup>1,2,18</sup> PLE and PB are independent risk factors for mortality in Fontan patients and their management is extremely challenging because of the limited treatment options.<sup>17</sup> However, these complications tend to recover spontaneously after HTx.<sup>1,4,5,17</sup> PLE is characterized by hypoproteinemia due to the excessive loss of serum proteins at the gastrointestinal level in parallel with abnormalities in calcium metabolism, loss of coagulation factors and immunoglobulins, and lymphopenia.<sup>4,18</sup> PLE presents clinically as ascites, peripheral edema, pleural and pericardial effusions, and malabsorption,<sup>4,5,18</sup> whereas PB may lead to severe ventilation impairment due to thick, rubbery, fibrin casts of the bronchi.<sup>4,5</sup>

The chronically elevated venous pressure and suboptimal cardiac output of the Fontan circulation negatively affect liver perfusion and drainage, thus causing hepatic injuries and chronic liver congestion.<sup>1,4,19,20</sup> The role of FALD is controversial. The large discussion regarding the assessment of the clinical condition of patients with FALD demonstrates that it may represent both an indication and a contraindication to HTx.<sup>4,17</sup> Indeed, FALD is also one of the major causes of heterogenous liver outcomes after 1 year post-HTx.<sup>21</sup>

Reliable prognostic markers for HTx candidacy are currently lacking.<sup>1,20</sup> FALD may be associated with different manifestations, such as hepatic congestion, fibrosis, cirrhosis, focal nodular hyperplasia, hypervascular lesions, hepatocellular carcinoma, portal hypertension, varices, and ascites.<sup>2,4,5,19</sup> Although a clear consensus is missing in the definition of FALD, cutoff values for most of the relevant parameters, laboratory data, and imaging assessments can be generated to evaluate the status of liver disease and hepatic damage. FALD patients normally present with altered levels of liver enzymes, bilirubin, serum proteins, and albumin.<sup>20</sup> Thrombocytopenia is associated with portal hypertension and gives an indication of liver fibrosis and splenomegaly.<sup>19,20</sup> High MELD-XI scores correlate with liver fibrosis,<sup>19</sup> higher risk of cardiac mortality or transplantation,<sup>22</sup> and poor early post-HTx outcomes.<sup>23</sup> Yang et al.<sup>24</sup> reported that patients with a MELD-XI score of less than 17 had an improved survival overall and while on VAD support. Furthermore, the score decreased in some VAD patients while on support. In these patients, the resulting post-HTx outcomes were similar to those of patients without liver dysfunction.<sup>24</sup>

The VAST score was introduced by Elder et al.<sup>25</sup> to characterize portal hypertension. Their study verified that Fontan patients with a VAST score greater than or equal to 2 were at higher risk of death, were more likely to require a transplant, and were at higher risk of developing hepatocarcinoma. Furthermore, using a modified version of the score (i.e., Varices, Ascites, Splenomegaly – VAS) showed that patients presenting with at least two of these features, oxygen desaturation and the need for a pacemaker, were at significantly greater risk of death and need for HTx.<sup>26</sup> Recently, Rodriguez et al.<sup>27</sup> assessed a combination of parameters as risk factors for isolated HTx short-term outcomes. This study reported that FALD patients with pre-HTx MELD < 15, MELD-XI < 16, Fontan liver magnetic resonance imaging (MRI) score < 10, and VAST score ≤ 2 achieved successful short-term outcomes after isolated HTx.<sup>27</sup>

The most effective imaging-based assessment of the liver is ultrasonography.<sup>19</sup> Indications for advanced liver disease are given by specific findings, such as the presence of surface nodularity, heterogenous parenchyma, fistulas, dilated portal veins, and splenomegaly.<sup>19</sup> Liver stiffness as determined by transient elastography correlates with the presence of fibrosis and allows for patient staging without the need for invasive biopsies<sup>19</sup> and for monitoring of FALD progression.<sup>28</sup> Murtuza et al.<sup>29</sup> showed that patients with preserved

ventricular function and moderate-to-severe liver fibrosis or VAST  $\geq 2$  were at higher risk of death.

Impaired renal function is an important consideration in the failing Fontan cohort, although it is less discussed than FALD.<sup>17</sup> Renal failure is often underrecognized in diagnosis and thus appears to be a rare complication.<sup>1,4,17</sup> As with liver disease, in Fontan patients the decreased cardiac output and venous congestion are considered causative of renal failure and chronic kidney disease.<sup>1,4,17</sup> The results of a recent meta-analysis are in line with these findings.<sup>30</sup> The study systematically reviewed failure of the Fontan system and risk of mortality in HTx. Risk of death was associated with chronic kidney disease, leading to a relative risk ratio of 5.8. The authors argue that chronic kidney disease lesions can become more acute in the immediate postoperative period, during ischemia, and in postsurgical low-output syndrome.<sup>30</sup> Consistent with these results, pre-HTx renal failure is a strong predictor of early post-HTx mortality.<sup>17</sup> To prevent irreversible kidney disease, it is tempting to improve kidney function prior to HTx by means of EXCOR® VAD therapy with VC-assisted circulation. The RegiVe registry monitors the status of renal impairment by the serum levels of blood urea nitrogen and of creatinine<sup>1</sup> and will provide further insight into the impact of preconditioning a failing Fontan patient on post-HTx outcome.

In addition, this study will investigate the length of the cardiopulmonary bypass during surgery. CHD patients require longer cardiopulmonary bypass and ischemic times,<sup>31</sup> leading to extended postoperative hospital stays. Use of the VC is thought to reduce the time needed to complete the challenging and complex surgery. The need for preparation of customized grafts and patches to reconstruct the missing connections and structures is eliminated and the duration of the cardiopulmonary bypass and ischemic time can be cut to a minimum. The VC can be implanted following a standardized procedure with the assistance of a virtual fitting session in the preparation phase.

## Limitations

This study has limitations inherent in all registry studies, including data entry errors and the bias and missing data introduced by voluntary data contribution. The study does not allow for imputations of potential missing data due to practice variation between investigational sites. As the failing Fontan circulation is a complex clinical condition, it is tempting to speculate about a heterogeneous patient cohort. The sample size was selected to gain early data from real-life scenarios; however, this non-interventional study does not allow for confirmative conclusions. The study data will be analyzed by means of descriptive statistics.

## Conclusion

To our knowledge, this is the first study evaluating the use of a medical device specifically developed for the subpulmonary support of failing Fontan patients as part of VAD therapy. The observational nature was selected to gather

data from real-life scenarios. In this setting, the study aims to investigate the most relevant aspects of this patient population (from cardiac function to end-organ status, QoL, survival to HTx, and safety outcomes) to assess the feasibility of the VC and EXCOR® VAD in replacing the missing subpulmonary ventricle. The results of the study will provide important insights into and further information on this vulnerable CHD cohort and their management in the context of dedicated VAD therapy. The findings will help to further develop VAD therapy by addressing the requirements of individual patients and tailoring treatment to their physiologies.

## Note

The study concept has been presented at the 50th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery (DGTHG); online; February 26<sup>th</sup> to 28<sup>th</sup>, 2021 [Menon et al, *Thorac Cardiovasc Surg* 2021;69(S 01)].

## Author's Contribution

O. M., F. D. R., and A. K. M. devised the medical rationale for this novel treatment option. E. D. S., T. S., K.-J. S., and A. K. M. elaborated the conceptual study design. The expert panel "European EXCOR® Pediatric Investigator Group" (EEPIG) contributed with intensive discussion and mutual agreement. E. D. S. prepared the manuscript, and all other authors contributed by thorough manuscript review. The authors thank Mr. Samuel Alberman for editing the manuscript.

## Conflicts of Interest

E. D. S., T. S., K.-J. S., and A. K. M. are employees of Berlin Heart GmbH. O. M. and F. D. R. received fees as EEPIG chairs. F. D. R. is proctor of Berlin Heart GmbH.

## References

- 1 Rychik J, Atz AM, Celermajer DS, et al; American Heart Association Council on Cardiovascular Disease in the Young and Council on Cardiovascular and Stroke Nursing. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation* 2019;140:CIR0000000000000696
- 2 Clift P, Celermajer D. Managing adult Fontan patients: where do we stand? *Eur Respir Rev* 2016;25(142):438–450
- 3 Poh CL, d'Udekem Y. Life after surviving Fontan surgery: a meta-analysis of the incidence and predictors of late death. *Heart Lung Circ* 2018;27(05):552–559
- 4 Elder RW, Wu FM. Clinical approaches to the patient with a failing Fontan procedure. *Curr Cardiol Rep* 2016;18(05):44–47
- 5 Kenny LA, DeRita F, Nassar M, Dark J, Coats L, Hasan A. Transplantation in the single ventricle population. *Ann Cardiothorac Surg* 2018;7(01):152–159
- 6 Riggs KW, Broderick JT, Price N, Chin C, Zafar F, Morales DLS. Transplantation for congenital heart disease: focus on the impact of functionally univentricular versus biventricular circulation. *World J Pediatr Congenit Heart Surg* 2021;12(03):352–359
- 7 Bryant R III, Morales D. Overview of adult congenital heart transplants. *Ann Cardiothorac Surg* 2018;7(01):143–151
- 8 Reid CS, Kaiser HA, Heinisch PP, Bruelisauer T, Michel S, Siepe M. Ventricular assist device for Fontan: who, when and why? *Curr Opin Anaesthesiol* 2022;35(01):12–17

- 9 Buratto E, Shi WY, Ye XT, Konstantinov IE. Ventricular assist devices for the failing univentricular circulation. *Expert Rev Med Devices* 2017;14(06):449–459
- 10 Griselli M, Sinha R, Jang S, Perri G, Adachi I. Mechanical circulatory support for single ventricle failure. *Front Cardiovasc Med* 2018; 5:115
- 11 Villa CR, Alsaied T, Morales DLS. Ventricular assist device therapy and Fontan: a story of supply and demand. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2020;23:62–68
- 12 Prêtre R, Häussler A, Bettex D, Genoni M. Right-sided univentricular cardiac assistance in a failing Fontan circulation. *Ann Thorac Surg* 2008;86(03):1018–1020
- 13 Moosmann J, Dittrich S, Purbojo A, Cesnjevar R. RVAD implantation in a Fontan patient with protein-losing enteropathy as a bridge to transplant: Prêtre modification. *J Card Surg* 2020;35(07):1721–1724
- 14 Nathan M, Baird C, Fynn-Thompson F, et al. Successful implantation of a Berlin heart biventricular assist device in a failing single ventricle. *J Thorac Cardiovasc Surg* 2006;131(06):1407–1408
- 15 Valeske K, Yerebakan C, Mueller M, Akintuerk H. Urgent implantation of the Berlin Heart Excor biventricular assist device as a total artificial heart in a patient with single ventricle circulation. *J Thorac Cardiovasc Surg* 2014;147(05):1712–1714
- 16 Michel SG, Menon AK, Haas NA, Hörer J. Cavopulmonary support with a modified cannulation technique in a failing Fontan patient. *Interact Cardiovasc Thorac Surg* 2022;35(02):ivac090
- 17 McCormick AD, Schumacher KR. Transplantation of the failing Fontan. *Transl Pediatr* 2019;8(04):290–301
- 18 Al Balushi A, Mackie AS. Protein-losing enteropathy following Fontan palliation. *Can J Cardiol* 2019;35(12):1857–1860
- 19 Téllez L, Rodríguez-Santiago E, Albillos A. Fontan-associated liver disease: a review. *Ann Hepatol* 2018;17(02):192–204
- 20 Daniels CJ, Bradley EA, Landzberg MJ, et al. Fontan-associated liver disease: proceedings from the American College of Cardiology Stakeholders Meeting, October 1 to 2, 2015, Washington DC. *J Am Coll Cardiol* 2017;70(25):3173–3194
- 21 Ybarra AM, Khanna G, Turmelle YP, et al. Heterogeneous outcomes of liver disease after heart transplantation for a failed Fontan procedure. *Pediatr Transplant* 2021;25(08):e14094
- 22 Assenza GE, Graham DA, Landzberg MJ, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. *Heart* 2013;99(07):491–496
- 23 Grimm JC, Magruder JT, Do N, et al. Modified Model for End-Stage Liver Disease eXcluding INR (MELD-XI) score predicts early death after pediatric heart transplantation. *Ann Thorac Surg* 2016;101(02):730–735
- 24 Yang JA, Kato TS, Shulman BP, et al. Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: use of the Model of End-stage Liver Disease (MELD) and MELD eXcluding INR (MELD-XI) scoring system. *J Heart Lung Transplant* 2012;31(06):601–610
- 25 Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. *Int J Cardiol* 2013;168(04):3764–3769
- 26 Elder RW, McCabe NM, Veledar E, et al. Risk factors for major adverse events late after Fontan palliation. *Congenit Heart Dis* 2015;10(02):159–168
- 27 Rodriguez DS, Mao C, Mahle WT, et al. Pretransplantation and Post-transplantation liver disease assessment in adolescents undergoing isolated heart transplantation for Fontan failure. *J Pediatr* 2021;229:78–85
- 28 Padalino MA, Chemello L, Cavalletto L, Angelini A, Fedrigo M. Prognostic value of liver and spleen stiffness in patients with Fontan associated liver disease (FALD): a case series with histopathologic comparison. *J Cardiovasc Dev Dis* 2021;8(03):30
- 29 Murtuza B, Hermuzi A, Crossland DS, et al. Impact of mode of failure and end-organ dysfunction on the survival of adult Fontan patients undergoing cardiac transplantation. *Eur J Cardiothorac Surg* 2017;51(01):135–141
- 30 Márquez-González H, Hernández-Vásquez JG, Del Valle-Lom M, et al. Failures of the Fontan system in univentricular hearts and mortality risk in heart transplantation: a systematic review and meta-analysis. *Life (Basel)* 2021;11(12):1363
- 31 Karamlou T, Hirsch J, Welke K, et al. A United Network for Organ Sharing analysis of heart transplantation in adults with congenital heart disease: outcomes and factors associated with mortality and retransplantation. *J Thorac Cardiovasc Surg* 2010;140(01):161–168