Pulsatile venous waveform quality in Fontan circulation-clinical implications, venous assists options and the future

Fontan dolaşımında pulsatil venöz dalga niteliği-klinik etkiler, venöz asist seçenekleri ve geleceği

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ABSTRACT

Objective: Functionally univentricular heart (FUH) anomalies are the leading cause of death from all structural birth defects. Total cavopulmonary connection (TCPC) is the last stage of the palliative surgical reconstruction with significant late hemodynamic complications requiring high-risk heart transplantation. Alternative therapeutic options for these critically ill patients are crucial. In Phase I, we investigated the effect of pulsatility of venous flow (VF) waveform on the performance of functional and "failing" Fontan (FF) patients based on conduit power loss. In phase 2, the effect of enhanced external counter pulsation on Fontan circulation flow rates is monitored.

Methods: In phase 1, Doppler VFs were acquired from FF patients with ventricle dysfunction. Using computational fluid dynamics (CFD), hemodynamic efficiencies of the FF, functional and in-vitro generated mechanically assisted VF waveforms were evaluated. In phase 2, Fontan circulation on sheep model was created and enhanced external counter pulsation (EECP) applied.

Results: Variations in the pulsatile content of the VF waveforms altered conduit efficiency notably. High frequency and low amplitude oscillations lowered the pulsatile component of power losses in FF VF waveforms. The systemic venous flow, pulmonary artery and aorta flows increased by utilizing EECP.

Conclusion: Our data highlighted the significance of VF pulsatility on energy efficiency inside SV circulation and the feasibility of VF waveform optimization. EECP assist in Fontan circulation can result in venous flow augmentation. *(Anadolu Kardiyol Derg 2012; 12: 420-6)*

Key words: Fontan, Fontan circulation, failing Fontan circulation, enhanced external counterpulsation, animal experiment, content of the VF waveforms

ÖZET

Amaç: Fonksiyonel tek ventrikül anomalileri tüm yapısal konjenital kalp anomalileri arasında beşinci en sık defekt olup, önde gelen bir ölüm sebebidir. Total kavopulmoner konneksiyon ameliyatı palyatif cerrahi rekonstrüksiyon ameliyatlarının en son basamağı olup, çoğunlukla kalp transplantasyonu gerektiren hemodinamik komplikasyonları mevcuttur. İleri derecedeki hasta bu kişilerde alternatif tedavi seçenekleri gereklidir. Çalışmamızın faz I evresinde, fonsiyonel ve bozulmuş Fontan dolaşımı olan hastalardaki kondüit enerji kaybı baz alınarak pulsatil venöz dalga niteliğini çalıştık. İkinci fazda ise, güçlendirilmiş eksternal kontrpulsasyonun Fontan dolaşımı akımları üzerindeki etkisini araştırdık.

Yöntemler: Faz I'de, ventriküler fonksiyon bozukluğu olan bozulmuş Fontan dolaşımı olan hastalarda Doppler venöz akımları analiz edildi. Bilgisayarlı akışkan dinamikleri yöntemiyle bozulmuş Fontan dolaşımının hemodinamik özellikleri ve venöz dalga niteliği değerlendirildi. Faz II' de Fontan dolaşımı gerçekleştirilen koyun modelinde güçlendirilmiş eksternal kontrpulsasyon uygulandı.

Bulgular: Venöz akım dalga niteliği pulsatilite ilişkisi tespit edildi. Bozulmuş Fontan dolaşımı olan hastalardaki yüksek frekans ve düşük amplitüdlü osilasyonların, venöz dalga niteliğindeki enerji kaybını azalttığı gösterildi. Güçlendirilmiş eksternal kontrpulsasyonun sistemik venöz, pulmoner arter ve aorta akımlarını artırdığı gösterildi.

Sonuç: Çalışmamız venöz akım pulsatilitesinin, sistemik venöz dolaşım içindeki enerji değişiklikleri açısından önemli olduğunu gösterdi. Güçlendirilmiş dışarıdan kontrpulsasyon venöz akım üzerinde artışa sebep olmaktadır. *(Anadolu Kardiyol Derg 2012; 12: 420-6)*

Anahtar kelimeler: Fontan, Fontan dolaşımı, bozulmuş Fontan dolaşımı, güçlendirilmiş eksternal kontrpulsasyon, hayvan modeli, venöz dalga niteliği

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Introduction

Single ventricle anomalies are the fifth most common heart defect and the leading cause of death from all structural birth defects in the United States. Staged-Fontan procedure is a successful palliation for children with single ventricle physiology. Although most patients with a Fontan circulation have a good quality of life for many years, a significant number of patients with single ventricle physiology have late hemodynamic complications, including ventricular failure, atrial arrhythmias, pleural and pericardial effusions and protein-losing enteropathy (1). The prospect of continuing late attrition after Fontan operation remains a genuine concern. For many of these patients, heart transplantation has become the next surgical "stage". However, donor shortage and the high-risk nature of transplantation for these complex and often very ill patients demand a search for alternative forms of treatment (2). Unfortunately, the progress to develop alternative surgical strategies for patients with single ventricle physiology has reached a plateau with minimally derived physiologic benefit from minute adjustments to surgical technique. This dramatic slowing of forward progress has resulted in the need for new therapeutic options, such as mechanical circulatory assist. The mechanical support options for a patient with Fontan physiology include extracorporeal membrane oxygenation (ECMO), biventricular assist device (biVAD) (which would necessitate bicaval cannulation or Fontan takedown) and single VAD support with fenestration closure or intra-aortic balloon pump (IABP) (3-5). Most centers operating on patients with congenital heart disease have favored the use of ECMO. The use of IABP has been restricted in congenital heart centers due in part to difficulties in management of counter pulsation in young patients, difficulty in insertion of the large sized commercially available devices in small children. The idea of Fontan-ventricular assist device (VAD) support contrasts sharply with the traditional concept of left or right VAD that generally takes over the circulatory responsibilities of a damaged ventricle. Preliminary data in humans and animals support the feasibility of pediatric VAD support, however, highlight the requirement for new strategies tailored specifically for functionally univentricular heart venous hemodynamics to decrease the venous stasis, restore the cardiac output (CO) and thereby extend the life of the entire cardiopulmonary circuit. Nevertheless, all the approaches are not without the need for significant invasive steps and are associated with significant morbidity in patients awaiting transplantation.

Previous studies focusing on functionally healthy patients after total caval pulmonary connection suggested the venae cavae flows and pressures to be biphasic complex waveforms (6-9). Recent attempts to quantify the pulsatility in Fontan patients revealed significant differences among different patient cohorts and suggested pulsatility as a promising parameter to predict late Fontan failure (10). Due to the absence of right heart active pumping source, minimized energy loss inside the total cavopulmonary connection (TCPC) pathway has been suggested for the best optimal surgical outcomes (11-14). In our study, as the phase I step, we investigated the caval flow dynamics and the associated changes in pathway power loss for failing Fontan patients. A new pulsatility index is proposed for quantifying the cavopulmonary flow pulsatility.

These preliminary investigations lead us to design an animal model as the Phase II of our study for examining the feasibility of alternative post-operative mechanical assist strategies that can enable favourable Fontan venous flow adjustments to improve the characteristic depressed hemodynamic state and gradually declining circulatory function in Fontan patients. We explored Fontan venous assist by retrofitting existing non-invasive systems based on enhanced external counter pulsation (EECP) after creating a right ventricular bypass on a sheep model. EECP therapy is a noninvasive outpatient therapy consisting of electrocardiography (ECG)-gated sequential leg compression, which produces hemodynamic effects similar to those of an intra-aortic balloon pump. However, unlike intra-aortic balloon pump therapy, EECP therapy also increases venous return. The second phase of our study aims to share our experience, surgical techniques, and preliminary data towards creating a successful ovine model for mimicking the Fontan circulation and studying optimal support strategies based on EECP therapy.

To date, all experimental attempts to establish complete right heart bypass in animals had failed, allegedly because (i) the circulatory force was not sufficient to drive the systemic venous return through the lungs without the right ventricular power source, (ii) staged "gradual" vascular remodeling was required to compensate the acute cardio-pulmonary hemodynamic changes from bi-ventricular circulations. Haller et al. (15) managed to bypass the right ventricle in three dogs in which a cavopulmonary anastomosis had been created and the tricuspid valve obliterated. They postulated that the right atrium was sufficient power source. Recently, Myers et al. (16) demonstrated stage-1 Fontan conversion in a juvenile sheep model by clamping the caval veins and maintaining systemic venous hypertension to study systemic adaptations in SV circulation and utility of cavopulmonary support as a bridge to neonatal Fontan repair (17).

Although the concept of counter-pulsation was introduced in the United States in the early 1950s, it took more than 40 years for investigators to develop the effective technology that is currently being used (18-20). Cuffs resembling oversized blood pressure cuffs-on the calves and lower and upper thighs, including the buttocks inflate rapidly and sequentially via computer-interpreted ECG signals, starting from the calves and proceeding upward to the buttocks during the resting phase of each heartbeat (diastole). This creates a strong retrograde counterpulse in the arterial system, forcing freshly oxygenated blood toward the heart and coronary arteries while increasing the volume of venous blood return to the heart under increased pressure. Just before the next heartbeat, before systole, all three cuffs deflate simultaneously, significantly reducing the heart's workload. This is achieved because the vascular beds in the lower extremities are relatively empty when the cuffs are deflated, significantly lowering the resistance to blood ejected by the heart and reducing the amount of work the heart must do to pump oxygenated blood to the rest of the body (18). A finger plethysmograms used throughout treatment to monitor diastolic and systolic pressure waveforms. Upon diastole, cuffs inflate sequentially from the calves, raising diastolic aortic pressure proximally and increasing coronary perfusion pressure. Compression of the vascular beds of the legs also increases venous return. Instantaneous decompression of all cuffs at the onset of systole significantly unloads the left ventricle, thereby lowering vascular impedance and decreasing ventricular workload. This latter effect, when coupled with augmented venous return, raises cardiac output. In summary, EECP therapy increases venous return, raises cardiac preload, increases cardiac output, and decreases systemic vascular resistance (21).

The first aim of the study is to evaluate the conventional and newly designed pulsatility indices for quantifying the cavopulmonary flow pulsatility. The second aim of the study is to design an animal model by creating Fontan circulation and the show the effect of EECP therapy on the venous and pulmonary artery flows.

Methods

Phase 1

Three patients with ages 22, 25 and 13 were studied. The operations had included end-to-side anastomosis of the superior vena cava (SVC) to the right pulmonary artery and an external cardiac conduit connecting the inferior vena cava (IVC) to the inferior surface of the right pulmonary artery in both patients. Two patients were New York Heart Association (NYHA) functional class III, and had the diagnosis of "failing" Fontan 14 and 7 years after TCPC. Prior to the examination, one patient developed major pulmonary arteriovenous malformations; both patients had ventricular systolic dysfunction, yet no clinical signs of protein losing enteropathy. Subjective assessment of ventricular systolic function by echocardiography indicated impairment. Magnetic resonance imaging (MRI) assessment of ejection fraction was not available. One patient was NYHA functional Class I and considered as a normal functioning Fontan patient. All patients were investigated by using multi-channel echocardiography on caval vessels synchronized with ECG and respiration (Fig. 1). Failing Fontan flow waveforms were recorded using with an Acuson 128XP/10 (Acuson, Mountain View, CA, USA) computed sonography incorporating a 2.5-MHz transducer during resting. Flow waveform pulsatility analysis was performed by using discrete number of harmonics to reconstruct the time dependent variation of venous flows by Fourier analysis, which is based on the general principle that periodic waveforms can be mathematically expressed as a sum series of pure sinusoidal harmonics. Alternative to the traditional pulsatility index, (22-24),

$$PI= \frac{Q_{max} - Q_{min}}{Q_{mean}}$$

we defined a new pulsatility index, i.e. total caval flow pulsatility index (TCPI), which integrates the instantaneous fluctuation of total caval flow from its mean along the respiration cycle. We test the hypothesis that PI is insufficient for accurately quantifying the pulsatility of Fontan venous flow waveforms, which are biphasic or multiphasic in nature. TCPI was defined as: where $Q_V(t)=Q_{IVC}(t)+Q_{SVC}(t)$ and. The caval flow waveforms appear periodic with a period; T referring to the length of the respiration cycle.

Likewise, the pulsatility of the individual caval flows were quantified using the index named as caval pulsatility index (CPI),

$$CPI^{IVC,SVC}= \frac{1}{T}\int_0^T \left| \frac{Q^{IVC,SVC}(t)}{Qo^{IVC,SVC}} -1 \right| dt$$

where, the subscripts and $Qo^{IVC,SVC}$ counts for time-resolved flows and time-averaged IVC, SVC flows, respectively. CPI was evaluated for each patient caval flows and compared with the traditional pulsatility formulation (PI) to test the above hypothesis.

Computational fluid dynamics simulations (FLUENT version 6.3.26 ANSYS Inc., Canonsburg, PA) were performed on the idealized one diameter offset TCPC geometry in order to illustrate

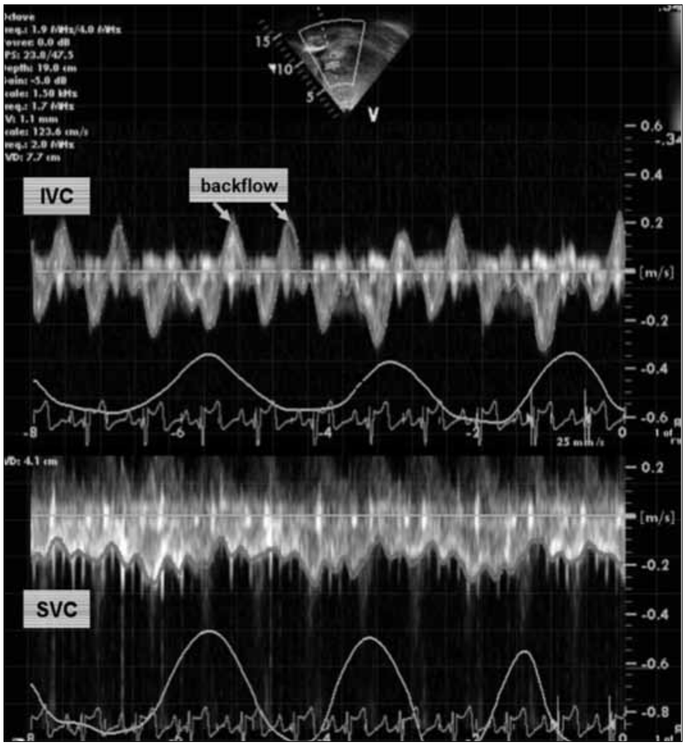

Figure 1. Raw pulse-wave caval Doppler recordings synchronized with the respiration of the "failing" Fontan patient 2.
IVC - inferior vena caval flow, SVC - superior vena caval flow

the effect of flow waveform pulsatility on energy loss independent from the effect of patient-specific surgical connection on energy loss. As higher flow rates generate higher energy losses (25), all waveforms were scaled to provide the same cardiac output value of 3 mL/min, which eliminated the mean cardiac output. The details of the computational model has been described previously by Dur et al. (26).

Scatter plots and statistical regression analysis were performed with MedCale Software Version 11.4.4 (Mariakerke, Belgium) to assess the strength and significance of the correlations between power loss and pulsatility indices. The study was approved by the institutional review boards of the University of Pittsburgh and performed at the University of Pittsburgh. Informed consent was obtained from all patients before study enrollment.

Phase 2

Three sheep weighing 60, 65 and 70 kg were used in this experiment. All animals received human care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (revised 1996, The National Academies Press). Texas A&M University, Institute for Preclinical Studies Institutional Animal Care and Use Committee (IACUC) approval was taken to perform the study at the Texas A&M University, Institute for Preclinical Studies.

Sheep were premeditated with Xylazine (0.15 mg/kg) and induction was performed with Ketamine (7.5 mg/kg) and Diazepam (0.375 mg/kg) followed by endotracheal intubation. The ventilation was set at a frequency of 12-15 breaths/min with a minute tidal volume of 10-15 mL/kg. Before any surgical incision is made, EECP cuffs were placed around the hind limbs and the hips. The cuffs then were connected to the EECP Console (Vasomedica Inc, Westbury, NY).

Right jugular vein and carotid artery were cannulated for continuously recording invasive pressures. Standard electrocardiography and rectal temperature were also monitored continuously.

After performing median sternotomy and pericardiotomy, gross anatomy was inspected and great vessels were dissected and isolated. Both azygos veins were ligated. SVC and IVC flow probes were placed around the native vessels. The Fontan circulation was established by introducing 27F metal tip, L-shape cannulas (dlp, Medtronics Inc.) both into the SVC and IVC. A third same size cannula was introduced into the distal main pulmonary artery. Three cannulas were connected to a Y-shaped connector. The characterization of the Y-shaped connector and cannula assembly was performed on bench-top experiments using blood analog glycerine-water solution. The resistance was found to be 1.2 mmHg mL/min and 1.4 mmHg mL/min at 3 and 4 LPM, respectively, which is comparable with that of actual extra-cardiac Fontan connection (27). A tubing probe was placed around the pulmonary artery cannula. A fourth probe was placed around the ascending aorta. The Fontan circulation was initiated by tightening the tourniquets at the levels of cannulas to divert the systemic venous return into the main pulmonary artery. A 12F vent was used to collect and return the coronary venous blood to the jugular vein.

Continuous flow measurements were performed by ultrasonic flow transducers (Transonic Inc., Ithaca, MA). Direct echocardiography was performed during pre-Fontan circulation; Fontan circulation and EECP treatment were recorded.

EECP treatment was performed at a routine 300mmHg cuff pressure.

Results

Phase 1

Our previous investigations indicated that caval flow waveforms in functional Fontan patients are comprised of 3 main harmonics (respiratory, cardiac and tertiary), Incorporating the same waveform decomposition protocol, the failing Fontan caval flows demonstrated significantly different characteristics (Fig. 2) (28, 29). In patient 1, cardiac and tertiary components were replaced by a series of smaller amplitude harmonics distributed over a large frequency band (Fig. 2). Likewise, major harmonics in patients 2 were also have relatively smaller amplitude harmonics over a higher frequency values.

Evaluation of proposed pulsatility indices (TCPI, CPI) for each waveform set indicated highest pulsatility for Functional Fontan case. TCPI for both failing Fontan patients was notably low in comparison to the Functional Fontan. Statistical analysis demonstrated a significant correlation between the TCPI and the hemodynamic power loss at fixed cardiac output value (Table 1).

Comparison of traditional and proposed time-integral pulsatility index evaluation indicated that six out of nine Fontan cavopulmonary waveforms fall outside the correlation with 95% confidence interval (Fig. 3). Comparing the relative pulsatile content of the selected cavopulmonary waveforms, the traditional pulsatility formula predicted relative pulsatility variation up to 70% error in comparison to the time-integral pulsatility scores.

Table 1. Total caval flow pulsatility index, caval flow pulsatility index, pulsatility index and power loss changes at fixed cardiac output value for functional and failing Fontan patients

Waveform	Power loss (mW)	TCPI	CPI		PI	
			SVC	IVC	SVC	IVC
Functional Fontan	8.43	0.64	0.14	0.46	1.3	1.1
Failing Fontan Patient 1	6.04	0.40	0.16	0.40	1.6	1.0
Failing Fontan Patient 2	6.83	0.55	0.17	0.42	1.1	2.1

CPI - caval flow pulsatility index, IVC - inferior vena cava, PI - pulsatility index, SVC - superior vena cava, TCPI - total caval flow pulsatility index

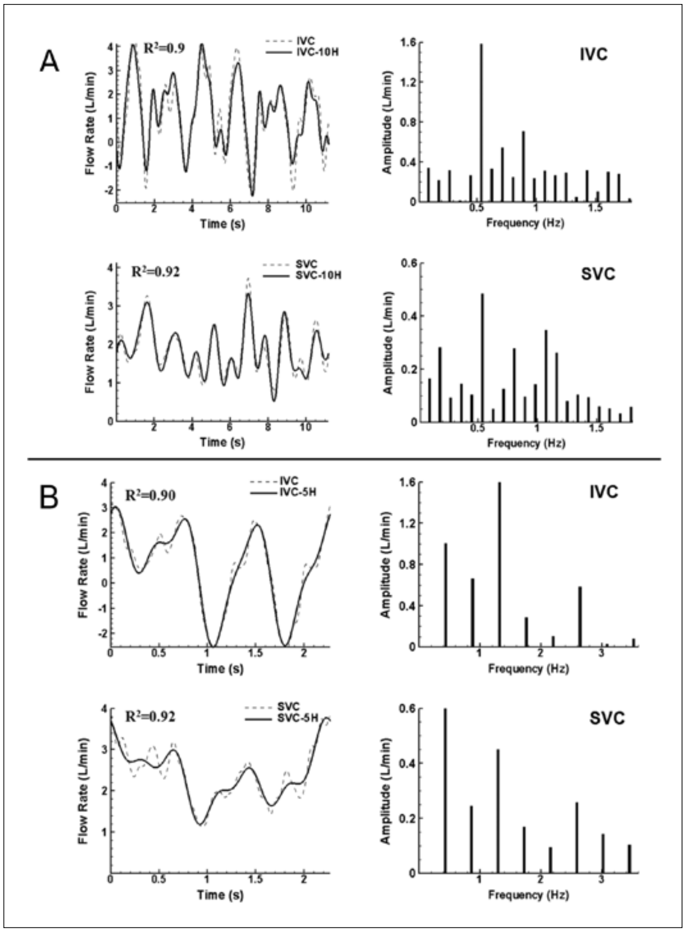

Figure 2. Doppler measurements of patient-specific "failing" caval flow waveforms (dashed lines) for patient failing Fontan 1 [A] and failing Fontan 2 [B] are reconstructed with discrete number of harmonic components (solid lines) with high accuracy (R^2=0.90). The full spectral decompositions of these waveforms are also provided on the right

IVC - inferior vena cavae, SVC - superior vena cavae

Phase 2

Baseline hemodynamic values were within the range (Table 2). After the initiation of the Fontan circulation by performing total right ventricular bypass, venous flow rates of SVC, IVC and pulmonary artery flows decreased significantly (Table 2). Heart rate and the mean arterial pressures were nearly identical to the baseline values. Direct echocardiography showed a minimal to moderate septal shift towards the right ventricle.

The pulmonary artery cannula of animal 1 came off during the measurements and this catastrophic event ended by terminating the experiment. Second animal showed a high amount of right ventricular filing despite the ligation of both azygos veins. The difficulty on decompressing the heart resulted a persistent ventricular arrhythmia and severe hemodynamic instability, which lead the investigators to terminate the study. Post-mortem analysis revealed an unexpected 3rd azygos system, which is connected directly to the coronary sinus posterior to the heart. EECP treatment was applied only to the third animal. A significant increase on the IVC, pulmonary artery and aortic flows was noted (Table 2).

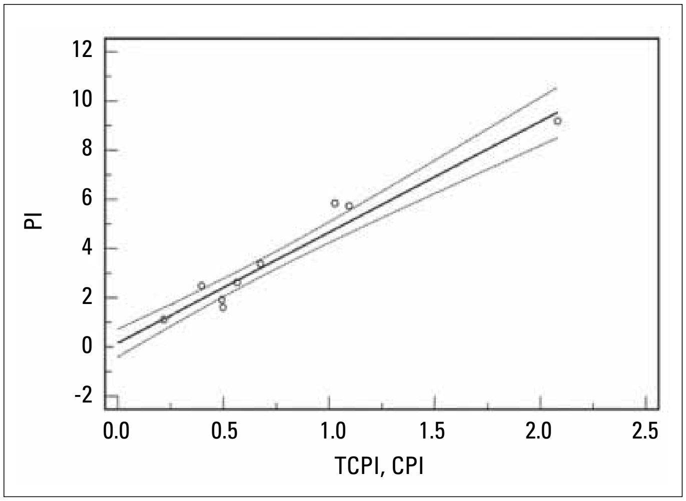

Figure 3. Comparison of the proposed time integral evaluation of pulsatility index, and traditional pulsatility index,

$$PI=\frac{Q_{max} - Q_{min}}{Q_{mean}}$$

indicated six out of twelve Fontan cavopulmonary flow waveforms fall outside of the correlation (R2 = 0.81) with 95% confidence interval (dotted curves). Traditional pulsatility formula predicted the relative pulsatility variation between the given cavopulmonary waveforms with up to 70% error in comparison to the time-integral pulsatility scores, and, refer to the instantaneous flow waveform, peak flow, minimum flow and time-averaged flow and period of the flow waveform, respectively

Discussion

In Phase 1, this study shows our proposed time integral approach is significant in quantifying the cavopulmonary pulsatility in Fontan patients. In Phase 2, this study shows the feasibility of Fontan circulation design in a sheep model and the positive contribution of EECP therapy on the venous flow rates.

Quantification of the energy efficiency of the *"failing"* waveform topology and flow dynamics studies may provide an additional hemodynamic parameter that can correlate with cardiac malfunction and postoperative complications.

Based on our hypothesis, we designed our study to understand and quantify the suboptimal physiological state of the failing Fontan patients by comparing the caval waveform dependent energetic of the functional and failing Fontan patients. Lower energy losses calculated for the failing Fontan patient compared to the functional Fontan with normalized cardiac output may be indication of an inherent cardio-adaptive management in order to reduce the strain on the malfunctioning single ventricle. Further analysis on larger patient cohort will identify this condition. Therefore, quantification of the energy efficiency of the failing waveform topology in terms of clinically meaningful indices may provide additional hemodynamic parameters that can correlate with the postoperative hemodynamic state. Future efforts will expand the limited real-time data through additional clinical studies for improved understanding of the venous energy efficiency throughout the disease timeline.

Table 2. Baseline, during Fontan circulation and EECP treatment with Fontan Circulation flow measurements of SVC, IVC, PA and AO

Animal Number	BASELINE						DURING FONTAN						DURING FONTAN AND EECP					
			FLOW						FLOW						FLOW			
	HR	MAP	SVC	IVC	PA	AO	HR	MAP	SVC	IVC	PA	AO	HR	MAP	SVC	IVC	PA	AO
1	102	95	4.0	3.4	3.9	3.9	104	90	2.0	1.0	2.9	3	100	95	*	*	*	*
2	107	85	3.1	3.6	3.8	3.6	110	80	2.2	1.2	2.4	3	111	84	*	*	*	*
3	100	82	4.0	3.6	4.0	4.1	104	78	2.1	1.1	2.3	2.9	105	80	*	5.0	3.2	4.0

Experiments were terminated before the EECP treatment in Animal 1 and 2. On animal 3, there is a significant increase on the IVC, PA and Ao flows after starting EECP treatment
AO - aorta, EECP - enhanced external counter pulsation, HR - heart rate, IVC - inferior caval vein, MAP - mean arterial pressure, PA - pulmonary artery, SVC - superior caval vein

Comparison of our proposed time integral approach and traditional pulsatility index indicated that the significance of using an integral approach to quantify the cavopulmonary pulsatility in Fontan patients. Previously we studied the pulsatile characteristics of venous flow waveforms that might be generated at inferior and superior caval vessels by venous assist therapies (26, 29). Clinically, it would be valuable to delineate user-friendly pulsatility parameters to show the conduit energetic the acute and long-term effect of venous assist options by determining the optimal performance characteristics of venous assist configurations on failing Fontan circulation.

EECP is a non-invasive circulatory assist system that augments systemic venous return and reduces ventricular afterload. We speculate that the indications of EECP treatment are fully in accord with the failing Fontan circulation. This study is to communicate the very early results of our ongoing animal experiments and to discuss our experience and pitfalls of creating an extremely challenging Fontan circulation on an ovine model. Early results of our experiments showed the feasibility of creating a Fontan circulation on a biventricular heart and the changes on the systemic venous and pulmonary flow. Previous studies demonstrate that the Fontan heart cannot use the compensatory mechanisms of the normal biventricular heart. Our animal model is confirming this state by using the flow indices. The increase in the systemic venous flow rate and the pulmonary artery flows show that implementing EECP treatment may contribute the Fontan flows to improve the venous return and lower the systemic afterload. To our knowledge, this is the first attempt to apply EECP treatment in Fontan circulation on an animal model. The only available study about the usefulness of external counter pulsation described an increase in cardiac index when applied immediately after postoperative period.

We developed an off-pump Fontan circulation model to mimic total cavopulmonary connection and demonstrated the proof of concept of EECP treatment. As dorsal positioning for ovine is not a preferred position for the lung ventilation and perfusion, for the next experiments PVR needs to be monitored and a lateral thoracotomy approach will be considered. Extra attention needs to be taken for the multiple azygos system on a sheep model. A ligation very close to coronary sinus can avoid the unwanted right ventricular filling by a different possible variety of azygos venous system.

The number of patients and the lack of MRI data in Phase 1, as well as the small sample size in Phase 2, are the limitations of the study. However, our proposed pulsatility indices described significant impact in quantifying the cavopulmonary pulsatility. The animal experiments are still in progress and this paper aims to show the feasibility of creating a Fontan circulation in a sheep model. Sample size is planned to expand which will help us to provide a more accurate evaluation of the effect of the EECP treatment on Fontan circulation.

Conclusion

Our phase 1 study indicated that the significance of venous pulsatility indices within total cavopulmonary connection geometry. The lower pulsatile energy loss state of failing Fontan patients may be an indication of an inherent cardiovascular adaptive mechanism in order to compensate the malfunctioning ventricle. In phase 2, our current preliminary in vivo sheep study showed the feasibility of creating a Fontan circulation without the help of cardiopulmonary bypass and the application and flow rate contribution of an EECP treatment on an animal model. Described waveform optimization and methods can tune and improve the venous assist therapy waveform quality. A future clinical study is designed as a phase III of the study protocol to evaluate the safety and the efficacy of EECP treatment in failing Fontan patients.

Conflict of interest: None declared.

Authorship contributions. Concept - E.K.; Design - E.K.; Supervision - E.T., Ö.S., M.W.M., T.W.F.; Resource - E.T.; Material - K.P.; Data collection&/or Processing - O.D., G.J.H.; Analysis &/or interpretation - E.K.; Literature search - P.D.W., V.O.M.; Writing - E.K., O.D., E.T., Ö.S.; Critical review - E.K., V.O.M., E.T.; Other - All authors.

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