# Classic pattern dyssynchrony is associated with outcome in patients with Fontan circulation

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## Abstract

### Background

Morbidity and mortality increase as Fontan patients age into adulthood. Limited studies have examined cardiac magnetic resonance and echocardiographic parameters to predict death and transplantation in children after Fontan operation. The aim of the study was to investigate echocardiographic parameters in adolescents and adults after Fontan operation including myocardial mechanics including classic pattern dyssynchrony (CPD) as predictors of transplantation or death.

### Methods

In a cross-sectional retrospective study, strain analysis was performed on echocardiography studies performed between 2001 and 2015 of 110 patients with single ventricle physiology after the Fontan procedure. Strain curves were measured and visually assessed for the presence of CPD. The primary end point was death or transplantation after a follow-up period of 85±35 months after echocardiography.

### Results

Median age at date of echocardiography was 20, range 3 to 45 years. Of 110 patients 28 patients were transplanted. During the study-period 3 patients died after transplantation and 7 patients died without being transplanted. CPD was seen in 16 and protein losing enteropathy (PLE) in 21 of 110 patients. By multivariate-analysis, CPD (HR 9.4 CI 2.6-34.6), PLE (HR 10.6 CI 3.4-33.2); systolic blood pressure (HR 0.954 CI 0.913-0.996), systolic/diastolic duration ratio (HR 6.83 CI 1.33-35.0) and E wave deceleration time (HR 0.98 CI 0.97 - 0.99) were independently associated with the primary end point.

### Conclusion

CPD, PLE, systolic and diastolic ventricular dysfunction are significantly associated with transplantation or death in Fontan operated patients. In selected patients, the presence of CPD may be a basis to investigate cardiac resynchronization therapy as a treatment strategy.

Keywords:
Classic pattern dyssynchrony
Strain imaging
Fontan operated patients
Transplant free survival

List of abbreviations
AVV: atrio-ventricular valve
BBB: bundle branch block
CPD: classic pattern dyssynchrony
E DT: E deceleration time
IVC: isovolumic contraction period
LAX: Long axis
PLE: protein losing enteropathy
SAX: short axis view
SDR: systolic/diastolic duration ratio
SR: strain-rate

## Introduction

Patients with single ventricle physiology comprise a complex and heterogeneous patient population, where the Fontan circulation constitutes a palliative life-prolonging procedure [1]. Over the past five decades, morbidity and mortality have been substantially reduced in childhood. Recent data report survival rates of 90% at 30 years of age and 80 % at 40 years [2-4]. However, despite continued advances in surgical techniques and improvements in patient care, Fontan patients exhibit the highest risk of death and complications among adolescents and adults with congenital heart disease (CHD)[5]. Many factors such as protein losing enteropathy (PLE), valvular dysfunction, thromboembolism, cardiac arrhythmias, Fontan obstruction and exercise intolerance have been identified as predictors of reduced survival [4, 6-8]. Furthermore, hypoplastic left heart syndrome and heterotaxy syndrome are known to increase short- and long-term risk of Fontan failure [7, 9]. Ventricular size and function are also of clinical importance, however there are only a limited number of studies supporting their association with outcomes [10-12].

In previous publications, we showed that the presence of classic pattern dyssynchrony (CPD) contraction patterns in adolescent and adult Fontan patients is associated with myocardial dysfunction, anatomical characteristics and ventricular geometry[13, 14]. However, little is known about myocardial function, mechanics and CPD and their association with outcomes in Fontan patients [15, 16]. Since CPD has been shown to be highly associated with reduced ventricular function, the present study aimed to investigate CPD, systolic strain, strain rate (SR) and diastolic SR in relation to transplant-free survival in Fontan patients.

## Methods

### Study subjects

From the Lucile Packard Children`s Hospital and Adult Congenital Heart Program at Stanford we identified patients with functionally univentricular heart diease (UVH) after Fontan palliation in a retrospective cohort study. All patients with UVH having undergone Fontan surgery and with echocardiograms available for review were included. Echocardiographic studies between 2001 and 2014 were reanalyzed. The study endpoints were transplantation or death, assessed after a follow-up period of 85±35 months (range 26-216 months) by the study end in 8/2020. Patients with missing endpoint- data at the end of the follow-up period were excluded from the study.

Cardiac morphology was retrieved from medical records. The distribution of UVH were classified by morphology type including two sizable ventricular or biventricular components (BV), single right ventricle (RV) or single left ventricle (LV). In cases of undefined RV, LV or BV anatomy, echocardiography was reassessed. Hearts not assigned to either group were labeled “undefined” single-ventricle anatomy (SV). Clinical data from the medical records, including ECG, blood pressure (BP), height, weight, body-mass index, exercise test with maximal oxygen uptake (VO2), New York Heart Association (NYHA) class, and presence of PLE were obtained from the same or the closest available to date of echocardiogram.

The study was conducted in accordance with institutional Human Subjects Committee guidelines and was approved by the Institutional Review Boards at Stanford University.

**Echocardiography**

Between January and May 2015 the latest available echocardiograms of Fontan-operated patients recorded at the Lucile Packard Children`s Hospital and Adult Congenital Heart Program at Stanford were selected for re-analysis. Images were acquired between January 2001 and May 2015 using a Philips IE 33 ultrasound scanner at Stanford Health Care or a Siemens Acuson 512 or SC 2000 ultrasound scanner at Lucile Packard Children`s Hospital at Stanford.

At least one apical and one short axis view (SAX) were available in the majority of studies. In these two projections, sagittal, transverse and longitudinal ventricular end systolic- and end diastolic diameters were measured using grey scale recordings.

Ventricular diastolic function was assessed from atrio-ventricular valve (AVV) pulsed-wave Doppler recordings measuring the maximal velocity of early filling (E)-wave and atrial contraction (A)-wave, AVV E wave deceleration time (E DT) and E/A ratio. We further calculated E/e` by using e` derived from speckle tracking displacement E-wave velocities from the basal segments in apical views. For the evaluation of AVV regurgitation and aortic regurgitation, we performed a multiparametric, semiquantitative approach as recommended in 2014 AHA/ACC Guidelines for Valvular Heart Disease[17].

**Two dimensional speckle tracking analysis for strain and SR**

Strain and strain-rate (SR) were analyzed offline from apical 4 chamber (4CH) equivalent views and a short-axis midventricular view using 2D Cardiac performance analysis version 1.1 (Tomtec Imaging Systems, Unterschleissheim, Germany) and Syngo VVI software (Siemens Medical Solutions, Mountain View, CA). At the time of analysis, both software packages used identical tracking algorithms and we performed identical extraction of values from registered strain-curves.

Images were acquired at framerates of 40 ±12 (range 30-93) frames/s. For strain and SR analysis, endocardial longitudinal and circumferential curves were used. Average longitudinal and circumferential strain and SR were derived from the endocardial trace of an apical long axis (LAX) and a parasternal SAX. Each projection of the ventricle was divided into six segments. When the septum was intact, the septum and lateral wall were segmented, excluding the lateral wall of the hypoplastic ventricle. In SV or BV anatomy strain-analysis was performed in the outer walls, while residual septum was not included.

Ventricular systolic and diastolic volumes and ejection fraction were calculated by the Simpson method derived from the endocardial trace of one long-axis 2D loop. Global or segmental strain-curves from missing endocardial segments or visually incorrect tracking due to subjectively low-quality images were discarded.

Timing of aortic valve opening and closure (AVC), AVV opening, E-wave termination and AVV closure were measured as time differences between Doppler flow in- and outflow using the ECG R-wave as a reference. For strain-analysis, the onset of the QRS-complex was used as time-point 0 for the onset of the cardiac cycle.

Based on Doppler-derived time measurements, using in-house customized software (based on an excel macro), segmental values for peak positive and peak negative strain were extracted during systole (QRS onset to AVC), while diastolic segmental SR and basal velocities were defined as peak values during E and A filling.

Tissue velocities were derived from displacement registrations of the medial and lateral wall basal segments from the apical 4CH view equivalent and expressed as the peak velocities from each segment and the mean of both values.

**Definition of classic pattern dyssynchrony**

Strain curves from the LAX and SAX projection were visually assessed. As described in a previous publication [13], **Figure 1** displays different patterns of segmental contraction. Panel B shows a variant which can typically be seen when contractile force in one or several segments is reduced. Here, some segments can display delayed shortening without conduction delay. The segments with reduced contractile force display initial stretching with delayed onset of shortening, a low slope of shortening and reduced peak-strain during systole. CPD (Panel C) is the typical electro-mechanical dyssynchrony pattern as originally described in patients with left bundle branch block (LBBB)[18, 19]. CPD segments with early electrical activation show early

shortening (also termed "flash"), with onset of the shortening during the isovolumic contraction period (IVC), followed by segmental stretch during early systole resulting in low end-systolic strain-values of the early activated segment. Segments affected by conduction-delay display early stretch starting with the contraction of the early activated segments, followed by delayed contraction. In CPD, segments with delayed activation display a steeper slope and typically reach higher end-systolic strain-values compared to early-activated segments. Early activation and stretch were defined to be present when two curves showed simultaneous shortening and stretching with a cut-off strain-value of at least -3% or + 3%. Panel D shows a deformation pattern when conduction-delay is present, but systolic strain-peaks are simultaneous, not dyssynchronous. This pattern is often seen in patients with pacemakers or BBB combined with the presence of preserved ventricular function. In contrast to CPD, early activated segments shorten during the entire duration of systole, up to, but not past AVC. Accordingly, patients were grouped into CPD and non-CPD groups. The non-CPD group included patients with normal (Panel A), regionally reduced function (Panel B) or conduction-delay with simultaneous peaks (Panel D).

**Statistical analysis**

Data are presented as mean ± standard deviation or proportion (%) as appropriate. $\chi^2$ tests for proportions or independent *t*-test continuous variables were used to compare variables between positive- and negative- endpoint groups. Univariable Cox regression analysis was performed for all parameters referring to the time period between the censuring date and time-point 0. This time-point was defined first as "date of echocardiography", second as "date of Fontan completion". No imputation for missing data was performed and multivariable analysis was done on all available patients for each analysis. The combination of parameters with $P < 0.05$ in a stepwise forward multivariable analysis was considered significant. Receiver operating characteristic analysis was performed for continuous variables to determine a cutoff value for

groups displayed in survival curves, adjusted for the other statistically significant factors in the multiple regression analysis. SPSS 26 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

## Results

### Patient characteristics

Of 152 Fontan patients, outcome data were available in 110 patients (72%) which included 79 patients from our prior study [13] and an additional 31 children with outcome data. There were 43 (39%) LV, 36 (33%) RV, 24 (22%) BV and 7 (6%) SV types of single ventricle morphology. Only 11 (10%) had an atriopulmonary Fontan while the remaining patients had either a lateral or extracardiac Fontan. The average follow-up period was 85±35 months. Median age at Fontan was 3 (inter quartile range (IQR) 2-6,5 years, range 1-25 years). Median age at echocardiography was 20 (IQR 12-27 years, range 3 to 45 years). The primary endpoint occurred in 35 patients, of which 28 were transplanted. Death after transplant occurred in 3 patients and death without transplant in 7 patients. **Table 1 and 2** show baseline clinical characteristics and echocardiographic parameters with and without the primary endpoint; respectively.

The presence of CPD was identified in strain-analysis in 16 patients. All 16 patients displayed CPD in SAX images, while 12 demonstrated CPD in both long- and short axis images. In all patients with CPD, systolic ventricular function was significantly reduced. Of the 16 patients with CPD, four had EF between 35 and 44%, in 6 patients EF was between 25 and 35% and in 6 patients between 12 and 25%.

In univariable analysis, PLE, NYHA class, lower BP, BV anatomy, lower longitudinal/transverse ventricular diameter ratio were associated with death/transplant (Table 3). Echocardiographic parameters including CPD, systolic and diastolic strain and SR

parameters and EF were significantly lower in Fontan patients with the primary end point. Higher E/A ratio and shorter E DT indicate higher filling pressures while a higher systolic/diastolic duration ratio (SDR) may indicate systolic and/ or diastolic dysfunction**.** **Table 3** shows univariate- and multivariate- Cox regression analyses revealing independent predictors for transplant-free survival. Clinical characteristics of PLE and BP and echocardiographic parameters of CPD, SDR, and E DT remained significant in multivariate analysis. Other strain and SR based parameters showed similar results in prediction of transplant or death in the multivariate approach when other correlating parameters were not entered into the equation. E DT, SDR and systolic BP as continuous variables were grouped and the adjusted survival-curves for the independent predictors are illustrated in **Figure 2**. Other strain and SR based parameters showed similar results in prediction of transplant or death in the multivariate approach when other correlating parameters were not entered into the equation. Among all systolic functional parameters, CPD was the strongest predictor of transplantation and death. PLE did not correlate with any of the functional parameters (R = -0.001; $p$ =0.940 for PLE and CPD).

**Figure 3** displays transplant-free survival for CPD and PLE for the time-period between Fontan completion and date of censuring. It is meant to illustrate the time-course of the disease in general when other various independent risk-factors are present, even though their presence was assessed at a later time-point.

**Reproducibility**

Results for the inter- and intra-observer variability of longitudinal strain measurements are published in our previous publication[13]. For the intra-observer variability for assessment of presence and absence of CPD the same reader reanalyzed the strain-patterns in 55 patients after a 6 weeks' period. For these analyses, all patients with previously diagnosed CPD (n=18) were included, while the other 37 patients were randomly chosen from the initial cohort of 152

Fontan patients. For the inter-observer variability, the same strain-curves were visually assessed by a second reader (SGD). The results are displayed in **Table 4**. The results of nine patients differed between two of the three repeated readings. In four cases, the early activated strain-curve was moderately reduced at the end of systole, representing moderate CPD which could be either assessed as CPD (Figure 1C) or dyssynchronous activation (Figure 1D). In the other five cases, the discrepancy of readings was caused by deviating interpretations of artificial segmental curves. Segmental artefacts were the main-reason for inter-observer variability, while moderate degree of dyssynchrony was present in three of the four discrepant intra-observer readings.

## Discussion

To the best of our knowledge, this is the first study showing that CPD is associated with an increased risk of death and transplant in patients after Fontan operation. Other echocardiographic parameters such as SDR and E DT suggest that evidence of systolic and diastolic dysfunction are also important risk factors for adverse outcomes. Furthermore, our study confirmed prior known risk factors such as PLE and low BP as predictors of adverse outcomes[20, 21]. As increasing number of Fontan patients age to adulthood, many of these individuals face significant morbidity and mortality. While clinical risk factors such as NYHA, PLE, arrhythmia, and thromboembolism are associated with death and transplant[22], these findings are typically found late in the course of Fontan failure. The identification of early echocardiographic parameters such as CPD offers an opportunity to detect high risks Fontan patients and possibly offer cardiac resynchronization therapy.

Prior studies have identified echocardiography and cardiac magnetic resonance imaging parameters as predictors of adverse outcomes in Fontan patients [10, 12, 15, 23, 24]. Ishizaki

et al demonstrated that GLS and a dyssynchrony index using CMR are predictors of adverse cardiac events in Fontan patients[15]. Global circumferential strain and ventricular end diastolic volume was demonstrated to be predictors of transplant free survival [15]. Previous studies did not specifically investigate the presence of CPD as a risk factor, which might have been an underlying unrecognized predictor for mortality in ventricles with reduced function.

**Classic pattern dyssynchrony**

In the present patient cohort, CPD was present in 60% of patients with two sizable ventricles with a large VSD, generally accompanied by a left anterior branch block with delayed electrical activation of the anterior wall. Like LBBB in normal anatomy, CPD in the single ventricle seems to be associated with both increased QRS width and unfavorable geometry including higher ventricular sphericity (increased transversal or sagittal diameter at shortened longitudinal diameter), and larger ventricular volumes[14]. Wall stress is mainly increased due to increasing wall stress at large ventricular dimensions.

CPDs typical contraction pattern originally described in patients with LBBB[18, 25, 26]. CPD is associated with true electro-mechanic delay at a stage of functional deterioration, indicating possible cardiac resynchronization therapy (CRT) response[19]. Thus, CPD constitutes a potentially reversible condition. Identifying CPD as a predictor of adverse outcomes renders new information for a patient group where CRT might be a risk reducing treatment option.

**Figure 1** demonstrates types of pathological contraction patterns differentiating between delayed onset and peak strain due to electrical activation delay as occurs in LBBB; or from reduced regional myocardial function without predominant electrical activation delay[13].

Panel B illustrates delayed peak strain due to reduced segmental contractility, while Panel C shows dysynchonous activation without the typical functional restriction of the early activated segment. In CPD (Panel B) early activated and shortening segments are followed by a typical

rebound stretch and significant loss of end-systolic strain. Even though time-to peak analysis is less specific for electro-mechanical dyssynchrony, a recent study showed that this parameter was highly predictive of major adverse cardiac events in patients with a Fontan-circulation[15].

The development of CPD in the single ventricular population remains unknown. The chronic volume overload prior to the Fontan operation may lead to late ventricular dilation and further decreases in systolic function. As such, delayed electrical activation may manifest from multifactorial causes including ventricular dilation and dysfunction, myocardial fibrosis, absence of ventricular-ventricular interactions or prior cardiac surgery[27-29]. CPD may be associated with lower cardiac output and higher Fontan pressure leading to adverse outcomes. While our study does not allow for assessment of causality, the association of electromechanical issues in the Fontan population with death and transplant is an important variable to better risk stratify and guide management of this vulnerable population.

**Predictors of long-term mortality**

In our study population, ventricular dyssynchrony correlated with ventricular dysfunction either measured by EF, global strain or SR[13]. Previous echocardiographic and MRI studies introduced several myocardial functional parameters as associated with high risk for Fontan failure including low global longitudinal and circumferential strain, cardiac volume index [10, 12, 15], and high brain natriuretic peptide [7, 9].

The present study further supports these previous findings by demonstrating that several systolic functional parameters such as longitudinal and circumferential strain and SR as well as early diastolic SR (E SR) were significantly associated with the primary endpoint[10, 12, 15]. Several predictors identified in our study, expressing either systolic (CPD, low BP, SDR) or diastolic dysfunction (SDR and E DT) are in line with these previous publications[10, 12, 15].

Even adjusting for the known relationship amongst CPD and low BP, shortened SDR and high filling pressures with shortened E DT[13], CPD was an independent predictor of death and transplant.

During the last four decades, the short- and long-term outcome of Fontan survivors have been substantially improved. However, patients with PLE, plastic bronchitis, Fontan associated cirrhosis, heterotaxy and right ventricular morphology remain at high mortality risk [4, 9]. In accordance with previous studies, our data showed PLE as the strongest predictor for transplantation or death, taking into account that not all known predictors could be measured. In summary, in addition to PLE as the most prominent risk- factor, the present study underlines the significance of CPD and ventricular dysfunction for deleterious outcome in Fontan patients.

**Clinical implication**

In non-CHD patients, CRT has become the treatment of choice when individuals with heart failure and ventricular dyssynchrony. Adding functional myocardial imaging to the common selection criteria for CRT has been shown to improve prediction of treatment-response and mortality[19, 30, 31].

Many Fontan patients will similarly develop chronic heart failure from a variety of etiologies including ventricular dysfunction. The cause of this ventricular dysfunction remains unknown but altered electromechanical coordination is likely one component of this. The complex anatomy and anatomic variation have limited the study of resynchronization therapy in this population. Zimmerman FJ et al[32] and Bacha et al[33] first demonstrated the utility of multisite pacing in the single ventricle population and demonstrated hemodynamic improvement. Subsequent reports of CRT in single ventricles have been included in larger series of CHD patients[34, 35] Boston Children`s Hospital reported 23 CRT implantation in Fontan- operated patients between 2004 and 2019, showing improved Tei-index and dP/dt as

an effect of CRT[36].Despite this literature, a German national registry-study reports only two registered patients with Fontan completion, having received a CRT[37] until 2018. A retrospective single center study from China reported 54 CHD patients with CRT implantation between 2004-2017, none with single ventricle physiology [38].

Pacemaker implantations in Fontan-patients are complex procedures. Lead dysfunction and pacemaker infection rates in CHD patients, especially with epicardial leads, are known to be disproportionally high[37, 38] and that implantation of permanent pacemakers in Fontan operated patients increase the risk of late death[7, 39]. The high complication rate and limited experience with dyssynchrony-assessment and CRT, have apparently resulted in a conservative treatment policy. However, gaining knowledge about the deleterious effect of untreated dyssynchrony in the Fontan population is important towards a more proactive management of Fontan patients with electro-mechanical delay. Additionally, the identification of echocardiographic parameters that may identify Fontan patients who would benefit from CRT is paramount to gaining the maximal benefit from this therapy. A recent publication on outcome on CRT treated patients with congenital heart disease, including 9 patients with UVH and propensity matched controls shows promising effect of CRT treatment, leading to improved transplant-free survival[40].

The present study showed that CPD was not only related to reduced myocardial function[13] but was also an independent predictor for death and transplant. The distinct effect in a small patient population points to CPD as an important risk factor in the management of Fontan patients in the long term. Careful selection of patients for CRT with the aid of functional myocardial imaging might have the potential to reverse heart failure, improve myocardial function and thus reduce mortality.

## Reproducibility

Interestingly, after 5 years, 15 out of 16 CPD positive patients of the first reading were re-identified as CPD in all three consecutive readings. Qualitative assessment of the repeated readings revealed two causes for deviating interpretation: First: curve-artefacts being revealed by non-physiological end-diastolic stretching seemed to invite for misinterpretations. In our study, artificial curves were the main-reason for false positive results in the inter-observer-variability. Assessment of curve-artefacts and their exclusion can probably increase reading-accuracy. The second cause for differing interpretation was a moderate degree of dyssynchrony, where the early-systolic strain curve showed dyssynchronous activation while the late systolic strain was only moderately reduced. These challenges need to be addressed in future by defining different grades of dyssynchrony and influence on outcome. In the present study, we searched for CPD in all patients, while we found CPD only present at prolonged QRS duration (mean, 142 msec; range, 104–195 msec)[13]. Thus, at short QRS duration, other reasons for changed strain-curves are more probable.

## Study limitations

The retrospective inclusion of patients with limited clinical data at time of echocardiography is a limitation. The absence of complete follow-up data is a limitation but only 28% of follow-up data were missing. Some known predictors of mortality like heterotaxy or indexed EDV and ESV were not consistently recorded and therefore not included. Furthermore, the echocardiography was not optimized for strain imaging, however SAX and long axis imaging loops were available in the majority of patients. The Lucile Packard Children Hospital and Stanford Health Care are transplant centers for pediatric and adult CHD patients, with a high percentage of complex cases referred for re-operation or transplant evaluation. Thus, transplant and mortality rate in this selected patient population were high and may not be representative for the general Fontan population. Selection of time-point of study entry is problematic for both,

time of "Fontan completion" and "date of echocardiography". However, our patient population was well suited to investigate clinical and functional predictors of long-term outcome in patients with Fontan completion.

Setting Fontan completion as date of study entrance does not include patients who were deceased or transplanted before the date of echocardiography. However, since all patients after Fontan surgery were followed with echocardiography, Fontan completion as the entrance date illustrates best the influence of PLE and CPD during the post-surgical course. Date of echocardiography reflects most appropriately the time of echocardiographic measurements including CPD assessment. However, is does not reflect the time-period between transplant or death and Fontan surgery. As mentioned above, echocardiography at the referring center was often associated with a referral for transplant assessment. Therefore, the occurrence of an echocardiogram and its timing may itself indicate a higher hazard for mortality or transplant. Following these considerations, we chose to present survival-curves referring to either entrance date.

Some earlier echocardiograms were recorded at low frame rates (25-35/s). Because of low frame-rates the presence of CPD may be missed if the typical initial contraction and rebound during the first 100 ms is not captured. This problem has become less frequent in newer ultrasound systems with improved frame-rates (50-100/s).

## Conclusion

CPD, PLE, systolic and diastolic ventricular dysfunction constitute important risk factors for transplantation or death in Fontan patients. Identification of CPD as a predictor for unfavorable outcome renders important information towards implementation of CRT as a treatment option in select Fontan patients.

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Table 1: Patient characteristics

| | Transplant-free Survival N % mean ±SD (N=75) | Death or Transplant N% mean ±SD (N=35) | *p*-value |
|---|---|---|---|
| **Male Gender** | 40 (53) | 23 (66) | 0.185 |
| **Female Gender** | 35 (47) | 12 (34) | |
| **Age at Fontan (years)** | 5.8±5.9 | 4.2±4.3 | 0.072 |
| **Age at echocardiography (years)** | 22±10 | 17±8 | **0.006** |
| **Protein Losing Enteropathy** | 8 (11) | 13 (37) | **<0.0001** |
| **Classic Pattern Dyssynchrony** | 7 (9) | 9 (27) | **0.007** |
| **Pacemaker** | 8 (11) | 4 (11) | **0.570** |
| **BP sys (mmHg)** | 111±15 | 104±13 | **0.004** |
| **BP dia (mmHg)** | 67±10 | 61±10 | **<0.0001** |
| **BMI (kg/m²)** | 22±8.6 | 21±7.2 | 0.296 |
| **Anatomy** | | | **0.021** |
| BV | 13 (17) | 11 (31) | **0.032** |
| LV | 33 (44) | 10 (29) | 0.112 |
| RV | 23 (31) | 13 (37) | 0.609 |
| SV | 6 (8) | 1 (3) | 0.162 |
| **Long/Trans Diameter Ratio ()** | 1.3±0.3 | 1.1±0.2 | **<0.0001** |
| **AV Valve Regurgitation grade I** | 53 (71) | 16 (46) | **0.083** |
| **AV Valve Regurgitation grade II** | 14 (19) | 7 (20) | |
| **AV Valve Regurgitation grade III-IV** | 0 (0) | 3 (9) | |
| **Aortic Valve Regurgitation grade I** | 37 (49) | 10 (29) | **0.295** |
| **Aortic Valve Regurgitation grade II** | 5 (7) | 3 (9) | |
| **Aortic Valve Regurgitation grade III-IV** | 0 (0) | 0 (0) | |
| **Type Fontan** | | | |
| RA to PA | 7 (10) | 4 (13) | 0.199 |
| Lateral tunnel | 23 (35) | 8 (25) | 0.716 |
| Extracardiac | 33 (50) | 18 (56) | 0.513 |
| Other | 3 (5) | 2 (6) | 0.636 |
| **QRS Duration (ms)** | 112±24 | 122±36 | **0.149** |
| **Fenestrated** | 19 (31) | 10 (35) | 0.732 |
| **NYHA** | | | |
| Class I | 16 (24) | 3 (9) | **0.003** |
| Class II | 41 (60) | 15 (46) | **0.003** |
| Class III | 11 (16) | 13 (39) | **0.003** |
| Class IV | 0 (0) | 2 (6) | **0.004** |
| **HR (bpm)** | 77±15 | 83±18 | **0.003** |
| **Systole/Diastole Ratio ()** | 0.95±0.31 | 1.1±0.28 | **0.008** |

EF: ejection fraction; BV: two sizable ventriclular components, mostly patients with unbalanced atrioventricular canal; LV: left ventricular; RV right ventricular; SV: single ventricle; RA to PA: right atrium to pulmonary artery; BP: blood pressure; BMI: body mass index; BSA: body surface area; HR: heart rate; Long: longitudinal; Circ: circumferential; SR: strain rate; LVOT VTI: left ventricular outflowtract velocity time integral; E DT: E wave deceleration time; AV valve: atrioventricular valve

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Table 2: Echocardiographic parameters

| | Transplant-free Survival N % mean ±SD (N=75) | Death or Transplant N% mean ±SD (N=35) | *p*-value |
|---|---|---|---|
| **EF (%)** | 46±14 | 34±15 | **<0.0001** |
| **Long/Trans Diameter Ratio ()** | 1.3±0.3 | 1.1±0.2 | **<0.0001** |
| **Long Strain sys (%)** | -14.1±4.5 | -9.9±6.1 | **<0.0001** |
| **Long SR sys ($s^{-1}$)** | -0.77±0.24 | -0.61±0.38 | **0.018** |
| **Long SR E ($s^{-1}$)** | 0.95±0.39 | 0.71±0.48 | **0.048** |
| **Circ Strain sys (%)** | -16±7 | -10±7 | **<0.0001** |
| **Circ SR sys ($s^{-1}$)** | -0.96±0.38 | -0.67±0.40 | **0.001** |
| **Circ SR E ($s^{-1}$)** | 1.22±0.81 | 0.81±0.51 | **0.016** |
| **LVOT VTI (cm)** | 17.1±6.8 | 16.2±7.4 | **0.145** |
| **Peak E velocity (cm/s)** | 68±24 | 73±27 | **0.077** |
| **E DT (ms)** | 168±70 | 132±44 | **0.002** |
| **E/A ratio ()** | 1.2±0.5 | 1.5±0.7 | **0.026** |
| ***E/e´sept ()** | 25±16 | 91±198 | 0.667 |
| **E/e´lat ()** | 99±152 | 99±147 | **0.066** |
| **Aortic valve regurge III-IV** | 5 (7) | 3 (10) | **0.085** |
| **AV valve regurge III-IV** | 8 (11) | 5 (16) | 0283 |
| | | | |

EF: ejection fraction; Long: longitudinal; Circ: circumferential; SR: strain rate; LVOT VTI: left ventricular outflow tract velocity time integral; E DT: E wave deceleration time; AV valve: atrioventricular valve

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| Table 3: Clinical and Echocardiographic Parameters Associated with Primary Endpoint | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable Cox regression analysis | | | | Multivariable Cox regression analysis | | | |
| | *p*-value | HR | CI lower bound | CI upper bound | P value | HR | CI lower bound | CI upper bound |
| | | | | | | | | |
| ***Protein Losing Enteropathy** | **<0.0001** | 4.14 | 1.99 | 8.62 | **<0.0001** | 10.6 | 3.4 | 33.2 |
| ***Classic Pattern Dyssynchrony** | **0.005** | 3.11 | 1.42 | 6.90 | **0.001** | 9.4 | 2.6 | 34.6 |
| ***EF (%)** | **<0.0001** | 0.96 | 0.93 | 0.98 | n.s. | | | |
| **Anatomy** | n.s. | | | | | | | |
| BV | | | | | | | | |
| LV | n.s. | | | | | | | |
| RV | n.s. | | | | | | | |
| SV | n.s. | | | | | | | |
| ***Long/Trans Diameter Ratio ()** | **<0.0001** | 0.088 | 0.024 | 0.329 | n.s. | | | |
| **QRS Duration (ms)** | n.s. | | | | | | | |
| **Fenestrated** | n.s. | | | | | | | |
| ***NYHA** | **0.020** | | | | n.s. | | | |
| Class I | | | | | | | | |
| Class II | **0.009** | 0.071 | 0.010 | 0.518 | n.s. | | | |
| Class III | **0.022** | 0.171 | 0.038 | 0.779 | n.s. | | | |
| Class IV | n.s | | | | | | | |
| **Age at Fontan (years)** | n.s | | | | | | | |
| ***BP sys (mmHg)** | **0.005** | 0.96 | 0.93 | 0.99 | **0.034** | 0.954 | 0.913 | 0.996 |
| **BP dia (mmHg)** | **0.001** | 0.94 | 0.91 | 0.98 | n.s. | | | |
| ***HR (bpm)** | **0.002** | 1.04 | 1.013 | 1.06 | n.s. | | | |
| ***Systolic/Diastolic Duration Ratio ()** | **0.007** | 3.8 | 1.45 | 9.97 | **0.021** | 6.83 | 1.33 | 35.0 |
| ***Long Strain sys (%)** | **<0.0001** | 1.13 | 1.05 | 1.20 | n.s. | | | |
| **Long SR sys ($s^{-1}$)** | **0.018** | 4.40 | 1.29 | 15.0 | n.s. | | | |
| **Long SR E ($s^{-1}$)** | **0.025** | 0.36 | 0.139 | 0.991 | n.s. | | | |
| **Circ Strain sys (%)** | **<0.0001** | 1.113 | 1.06 | 1.20 | n.s. | | | |
| **Circ SR sys ($s^{-1}$)** | **0.001** | 6.06 | 2.16 | 16.97 | n.s. | | | |
| **Circ SR E ($s^{-1}$)** | **0.001** | 0.394 | 0.162 | 0.727 | n.s. | | | |
| **LVOT VTI (cm)** | n.s. | | | | | | | |
| **Peak E velocity (cm/s)** | n.s. | | | | | | | |
| ***E DT (ms)** | **0.004** | 0.99 | 0.980 | 0.996 | **<0.0001** | 0.98 | 0.97 | 0.99 |
| ***E/A ratio ()** | **0.048** | 1.7 | 1.01 | 2.84 | n.s. | | | |
| ***E/e´sept ()** | **0.003** | 0.997 | 0.995 | 0.999 | n.s. | | | |
| **E/e´lat ()** | n.s. | | | | | | | |
| **Aortic valve regurgitation** | n.s. | | | | | | | |
| **Atrio ventricular valve regurgitation** | n.s. | | | | | | | |

*parameters entered into the multiple regression analysis
EF: ejection fraction; BV: two sizable ventriclular components, mostly patients with unbalanced atrioventricular canal; LV: left ventricular; RV right ventricular; SV: single ventricle; RA to PA: right atrium to pulmonary artery; BP: blood pressure; BMI: body mass index; VO2: ; HR: heart rate; Long: longitudinal; Circ: circumferential; SR: strain rate; LVOT VTI: left ventricular outflowtract velocity time integral; E DT: E wave deceleration time; AV valve: atrioventricular valve

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| Table 4: Repeated reading of 55 patients of the study | | | | |
|---|---|---|---|---|
| | First reading (AR) | | | |
| | | CPD+ | CPD- | Pearson`s R |
| Second reading (AR) (Intra-observer variability) | CPD+ | 19 | 3 | 0.849 |
| | CPD- | 1 | 32 | |
| Second reader (SGD) (Inter-observer variability) | CPD+ | 18 | 4 | 0.697 |
| | CPD- | 4 | 29 | |

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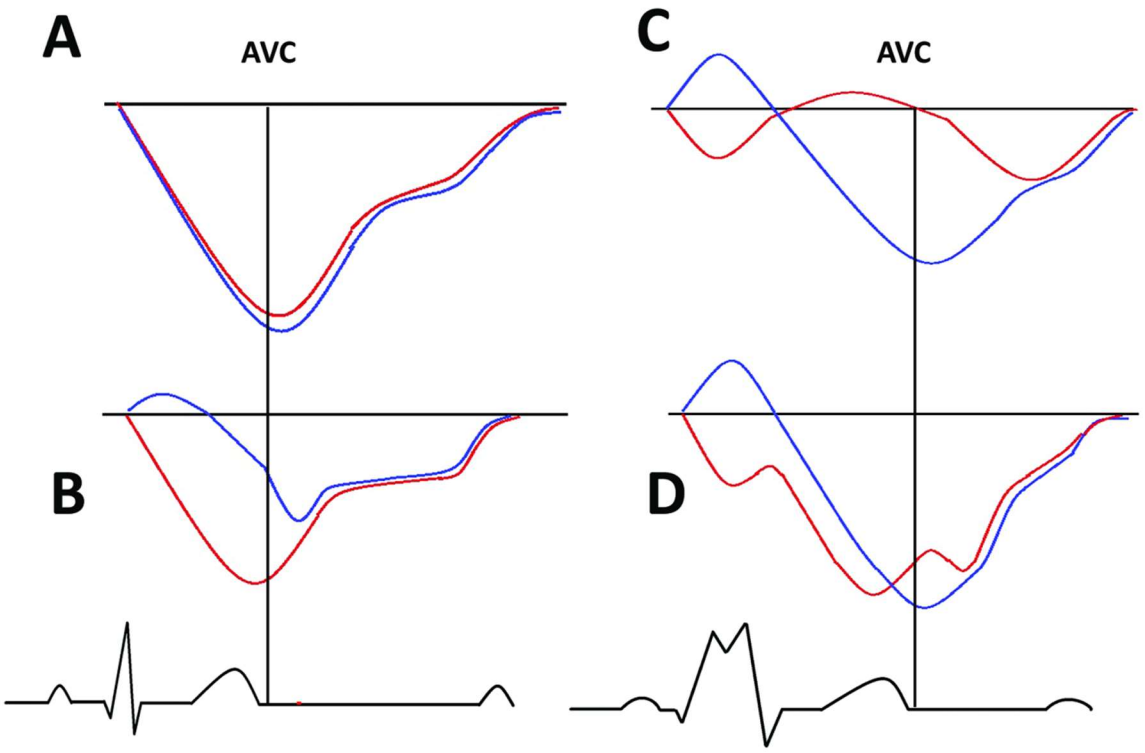



**Figure 1:**

Identification of typical contraction patterns in two opposite walls of one view: Panel A demonstrates normal contraction pattern with synchronous activation and little differing strain-peaks. Panel B shows a typical pattern at reduced myocardial function in the lateral wall. Even though the septum is contracting early, there is no early systolic rebound stretch. Panel C: CPD (classic pattern dyssynchrony) displays typically early shortening during systole (red marks the early activated segment), followed by a rebound-stretch and elongation of the same segment when the late activated segment (blue) contracts. Segments of the opposite wall (blue lines) elongate early in systole, shortening later in early systole and shorten still after aortic valve closure (AVC) due to a delayed relaxation phase. Panel D demonstrates dyssynchronous activation with synchronous end-systolic contraction. This pattern can be seen in hearts with ventricular pacing or prolonged QRS complex often in combination with preserved ventricular function. Here the typical early shortening of one wall and elongation of the opposite wall can be seen, while strain peaks of all walls approximately simultaneous. As seen in Panel B, C and D, the segment with lower end-systolic strain is followed by post-systolic strain.

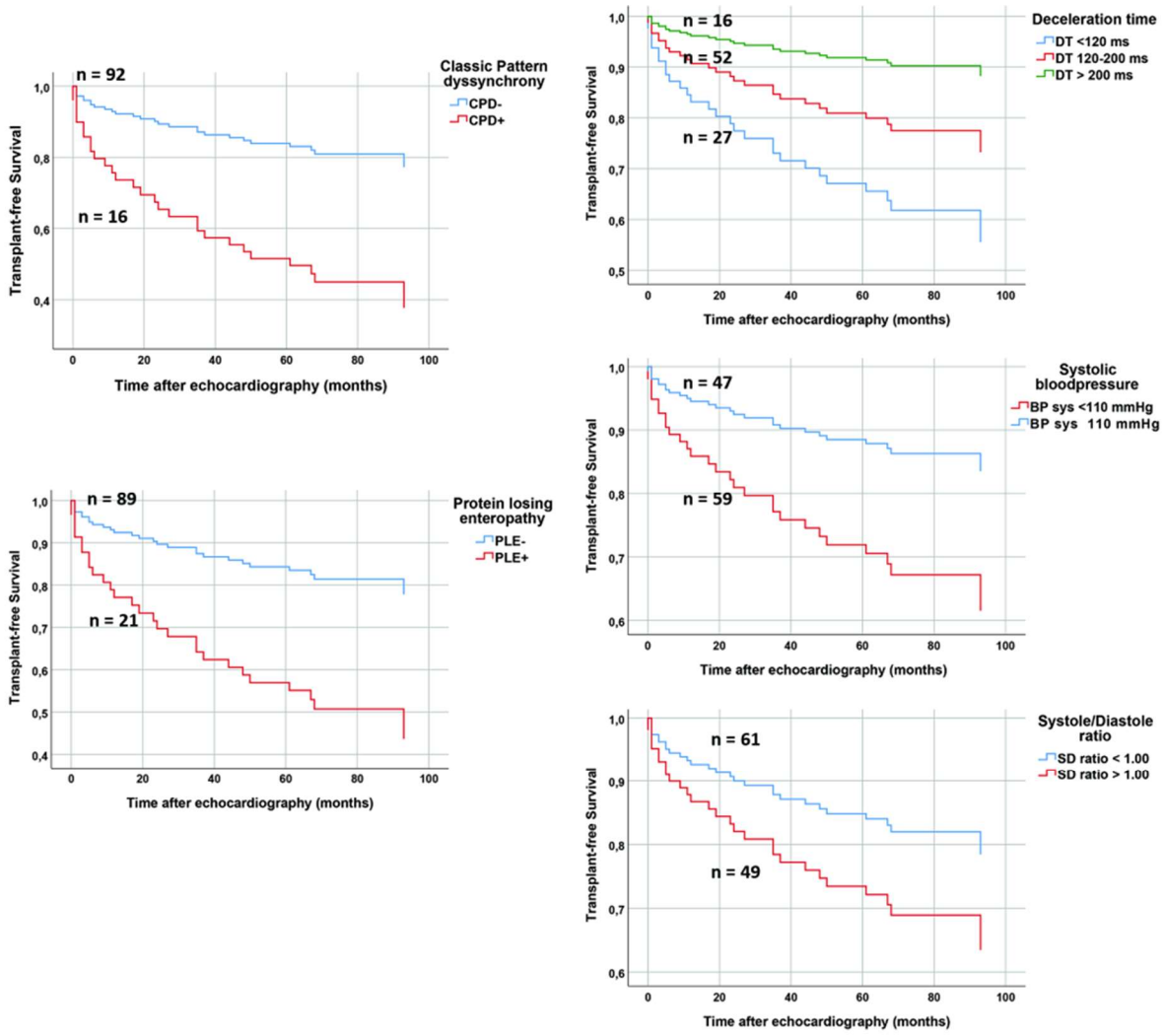
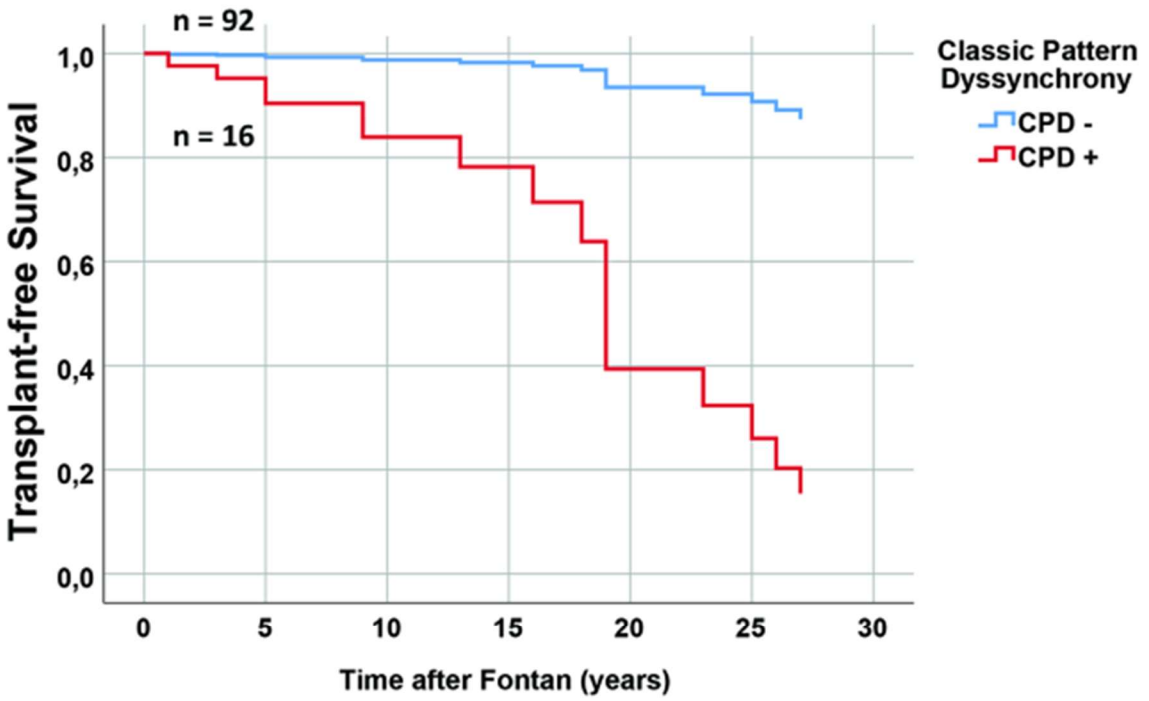
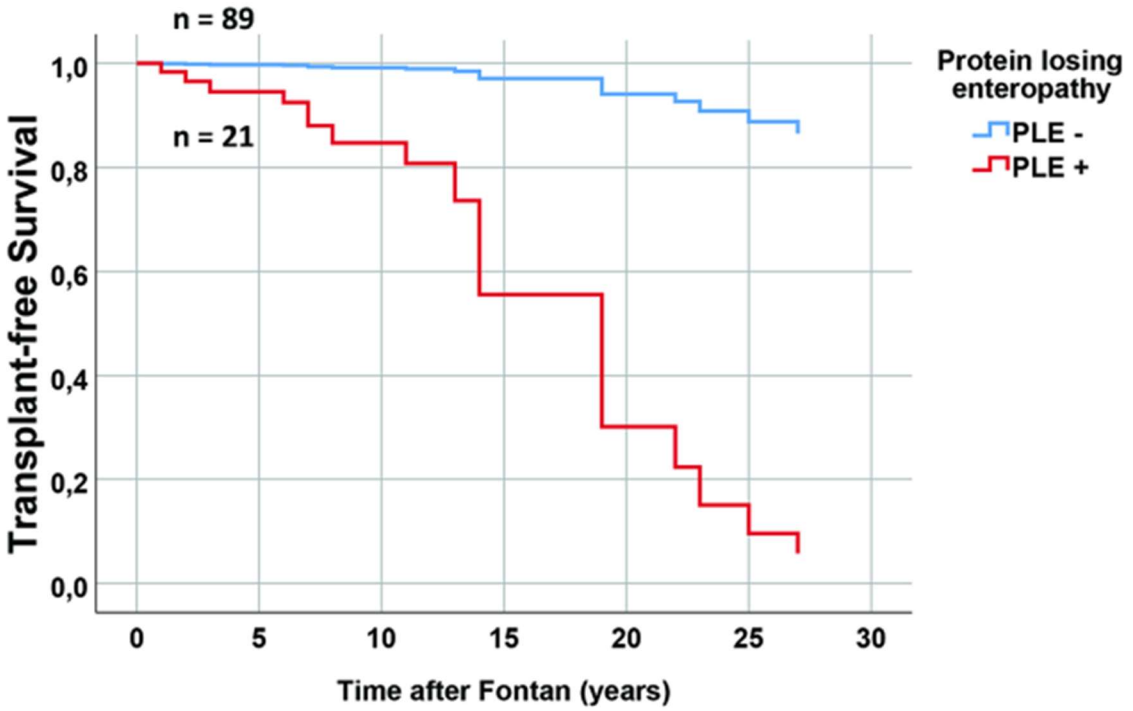



**Figure 2:** Cox regression survival charts for transplant-free survival in relation to date of echocardiography. All independent predictors of the Cox regression analysis are displayed as charts, each corrected for all other independent predictors. Echocardiographic parameters, classic pattern dyssynchrony (CPD), presence and absence of protein losing enteropathy (PLE) were recorded at the date of echocardiography.


n = 92
n = 16
Transplant-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
5
10
15
20
25
30
Time after Fontan (years)
Classic Pattern Dyssynchrony
CPD -
CPD +


n = 89
n = 21
Transplant-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
5
10
15
20
25
30
Time after Fontan (years)
Protein losing enteropathy
PLE -
PLE +

1

2

**Figure 3:** Cox regression survival charts in relation to Fontan completion displaying CPD and PLE corrected for the other independent predictors. This figure illustrates the time-course after Fontan surgery at the presence of (later occurring) risk factors.