Impaired systemic ventricular relaxation affects postoperative short-term outcome in Fontan patients

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Objectives: Systemic ventricular end-diastolic pressure has been used as a predictor of outcome in patients undergoing the Fontan operation. However, this index only evaluates late diastolic function and does not assess active ventricular relaxation during the phase of early diastole, a key component of systemic venous pathway flow. This study sought to examine whether impaired preoperative systemic ventricular relaxation, expressed as the time constant of isovolumic relaxation (τ), affects short-term postoperative outcome in Fontan patients.

Methods: All patients who underwent Fontan operation between May 1998 and November 2001 were enrolled. τ was calculated from digitized preoperative systemic ventricular pressure tracings. Standard preoperative invasive indices were also recorded and analyzed. These independent variables were then entered into a multiple stepwise regression model, with length of intensive care unit stay, length of hospital stay, and prolonged pleural effusion as outcome variables.

Results: Twenty-seven patients fulfilled inclusion criteria. Systemic left ventricle predominated, and all patients had undergone prior staged palliation. Extracardiac Fontan was the commonest operative technique. Of the independent variables examined, τ was the only statistically significant predictor of length of intensive care unit stay ($P < .001$) and length of hospital stay ($P = .002$). None of the independent variables predicted pleural effusion greater than 10 days.

Conclusions: τ was the only significant preoperative invasive predictor of short-term outcome in the Fontan patients. This illustrates the importance of systemic ventricular relaxation and highlights the need for a more comprehensive assessment of diastolic function before the Fontan operation.

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The Fontan operation has evolved over the past 30 years,^{1,2} and it is now indicated for the treatment of a variety of complex congenital heart defects with single ventricle physiology.³ Advances in operative technique and postoperative management have led to improved early survival rates in the modern era.⁴⁻⁷ Comprehensive retrospective analyses have led to better pre-Fontan management and patient selection, with various standard risk factors identified.⁸⁻¹⁰ However, despite careful evaluation of standard preoperative risk factors, postoperative outcomes remain variable.

The importance of maintaining systemic ventricular function in Fontan patients is well recognized. Both systolic dysfunction, as evidenced by increased end-systolic wall stress, decreased contractility, and reduced ejection fraction,¹¹ and diastolic dysfunction, as evidenced by increased ventricular end-diastolic pres-

sure,¹² have been identified as predictors of mortality. However, ventricular end-diastolic pressure reflects only the mechanics of late diastole and does not evaluate early diastolic filling properties, which have been shown to be important determinants of Fontan pathway flow.¹³ The rate of ventricular relaxation is the driving force behind early ventricular filling. This phase of diastole is typically assessed by measuring the rate of fall in ventricular pressure during isovolumic relaxation, expressed as the time constant of isovolumic relaxation, or tau. This study sought to determine whether preoperative systemic ventricular relaxation (quantified by tau), was predictive of postoperative short-term outcome in patients having the Fontan operation.

Methods

Study Population

The study group was compiled by retrospective review of all patients undergoing the Fontan operation between May 1998 and November 2001 at Cincinnati Children's Hospital Medical Center. Inclusion criteria required that only those patients who underwent preoperative cardiac catheterization at our institution were included, and the catheterization had to include a systemic ventricular pressure recording. This was to ensure uniformity of catheterization equipment, techniques, and data acquisition.

Preoperative Hemodynamics

Systemic ventricular pressure tracings were digitized offline with the use of a curve analysis program (Digisonics Curve Analysis Program; Digisonics, Houston, Tex). Left ventricular (LV) pressure data were sampled at 5-ms intervals. Left ventricular end-diastolic pressure (LVEDP) was measured at end-expiration, and peak negative rate of pressure rise (dP/dt) was calculated. Tau was calculated according to the method of Weiss and associates,¹⁴ using a semilogarithmic model (zero asymptote) with the true exponential decay starting at peak negative dP/dt and ending at 5 mm Hg above the LVEDP. All measurements were expressed as the average of three cardiac cycles. Pulmonary vascular resistance and transpulmonary gradient were calculated from invasive measurements by the Fick method, in the standard manner. The measurer was blinded to the outcome data when measuring the catheter-derived indices.

Postoperative Outcome

Short-term outcome variables included length of intensive care unit (ICU) stay in days, length of hospital stay in days, and prolonged pleural effusion greater than 10 days. In addition, we performed a logarithmic transformation (base 10) of the outcome variables of ICU and hospital stay in order to normalize their distribution.

Reproducibility

To validate our technique of pressure curve digitization, we investigated the relationship between tau values derived from fluid-filled catheters and those derived from micromanometer catheters in 10 biventricular patients (age, 6.6 ± 6.4 years). These patients underwent both fluid-filled catheter and micromanometer catheter

evaluations and had tau calculated from both sets of ventricular pressure recordings. This comparison study demonstrated good correlation between the 2 techniques, with the fluid-filled technique consistently underestimating tau by 3 ms (22.2 ± 2.9 ms vs 25.1 ± 2.5 ms). To assess intraobserver variability of tau measurements, 10 Fontan study patients had tau calculated on 2 separate occasions by the same observer (W.L.B.).

Data Analysis

Clinical outcome data and catheter-derived data were entered into an electronic database and analyzed with a statistical software package (SAS Institute Inc, Cary, NC). A *P* value of $< .05$ was considered statistically significant. The 4 independent variables—tau, LVEDP, pulmonary vascular resistance, and transpulmonary gradient—were entered into a multiple stepwise regression model, with ICU and hospital stay as dependent variables. The same 4 independent variables were analyzed by means of stepwise logistic regression to determine predictors of prolonged pleural effusion greater than 10 days. In addition, linear regression was performed to determine whether there was a significant relationship between crossclamp times and cardiac bypass times when compared with length of ICU and hospital stay.

Results

Patient Population

Twenty-seven patients, of a total of 33 patients undergoing the Fontan operation during the enrollment period, fulfilled inclusion criteria (age range, 2.5-25 years, mean age, 5.4 years). Patient demographics are displayed in Table 1. Two patients underwent revision of a previous classic Fontan, with refractory arrhythmias as their primary indication for surgery. Cardioplegic arrest was used in 12 patients.

Preoperative Hemodynamics

The study patients had favorable standard invasive preoperative hemodynamics (Table 1). The values of tau ranged from 9 to 45 ms, with a mean of 28 ms. Unfortunately, large studies looking at normal tau values are not available, especially for pediatric patients or in single ventricle patients. However, in an as yet unpublished study at our institution using ECHO determination of tau in patients with other echocardiographic evidence of diastolic dysfunction, a mean tau value of 44 ± 14.6 was measured, which is similar to what was found in the poorer outcome patients in this study. On the basis of evaluation of normal cardiac echocardiograms, we have set a value under 30 ms as being within a normal range.

Postoperative Outcome

The range of short-term clinical outcomes was broad. Six patients had a total hospital stay of longer than 2 weeks; within this group, 3 had pancreatitis develop, 2 had prolonged pleural effusions, and 1 had refractory arrhythmia as the major complication. There were 2 deaths, one of which was of a patient undergoing Fontan revision. By means of

TABLE 1

Patient characteristics	
Demographics	
Total patients	27
Age (y)	2.5–25 (mean = 5.4)
Ventricular morphology	
RV (HLHS, DORV)	7
LV (TA, DILV, PA)	20
Preoperative hemodynamics	
Pulmonary vascular resistance (W/m ²)	0.8–3.5 (mean = 2)
Transpulmonary gradient (mm Hg)	3–8 (mean = 5)
Ventricular end-diastolic pressure (mm Hg)	3–12 (mean = 6)
Tau (ms)	9–45 (mean = 28)
Prior palliative surgery	
BDG	20
Hemi-Fontan	5
Classic Fontan	2
Fontan type	
Extracardiac conduit	18
Lateral tunnel	7
Intracardiac tube	2
Fenestration	10
Operative time	
Crossclamp (min)	0–111 (mean = 27.6)
Cardiac bypass (min)	37–295 (mean = 127.5)
ICU stay (d)	1–40 (median = 3)
Total hospital stay (d)	4–43 (median = 12)
Pleural effusion > 10 d (patients)	11

RV, Right ventricle; HLHS, hypoplastic left heart syndrome; DORV, double-outlet right ventricle; LV, left ventricle; TA, tricuspid atresia; DILV, double-inlet left ventricle; PA, pulmonary atresia; BDG, bidirectional Glenn; ICU, intensive care unit.

linear regression, there was shown to be no significant relationship between the length of ICU and hospital stay when compared with duration of crossclamp or cardiac bypass times. The effect of fenestration on length of ICU and hospital stay was assessed by performing *t* tests between the fenestrated and nonfenestrated group, and no significant difference was found (*P* values of .56 and .44, respectively). Of the 11 patients with prolonged pleural effusions, 4 were fenestrated, and 7 were nonfenestrated. However, the decision to fenestrate is often made in the operating department based on intraoperative hemodynamics and thus may result in a selection bias between these 2 groups.

Preoperative Hemodynamics Versus Postoperative Outcome

Multiple regression analysis of the 4 independent variables derived from preoperative cardiac catheterization (tau, transpulmonary gradient, pulmonary vascular resistance, and systemic ventricular end-diastolic pressure) revealed that tau was the only independent predictor of length of ICU stay that reached statistical significance (*P* < .001, Figure 1). With length of total hospital stay as the outcome vari-

Figure 1. Relationship between the time constant of isovolumic relaxation (tau) and length of ICU stay (log. base 10).

able, again, only tau came out as being a statistically significant predictor (*P* = .002, Figure 2). By stepwise logistic regression, none of the 4 independent variables significantly predicted pleural effusion greater than 10 days. In addition, when fenestration was accounted for in the multiple regression model for ICU and hospital stay, and in the stepwise logistic regression for prolonged pleural effusion, it did not significantly alter the results. The mean and median heart rate during measurement of tau was 97 ± 16 and 95 ms, respectively. Heart rate, analyzed as an independent variable in multiple linear regression, was not a predictor of ICU or hospital stay. Nor did variation in heart rate affect the significance of tau as an independent variable. Unpaired *t* test showed no significant difference (*P* = .4) in heart rate between the poor outcome group (mean heart rate, 101 ± 10 beats/min) and the good outcome group (mean heart rate, 95 ± 17 beats/min).

Reproducibility

Pearson correlation coefficients between tau values derived from fluid-filled and micromanometer catheters showed agreement (*r* = 0.89, *P* < .001). The fluid-filled catheter values tended to be lower than those derived from the micromanometer catheter, however a Bland-Altman plot showed no significant systematic error. Intraobserver variability of calculated tau values in the Fontan patients was expressed by a significant Pearson correlation coefficient (*r* = 0.91, *P* < .001).

Discussion

This study demonstrates that preoperative tau values are an important predictor of postoperative outcome in single-ventricle patients undergoing the Fontan operation. Systemic ventricular relaxation appears to play an important

role in these patients, especially during the short-term postoperative period.

Fontan Outcomes

Continual evolution and refinement of both surgical techniques and postoperative management have led to reduced mortality rates in patients undergoing the Fontan operation.⁷ In addition, careful patient selection and the performance of earlier staged palliative procedures allow for optimization of pre-Fontan hemodynamics.^{15,16} However, despite these advances and careful attention to traditional preoperative risk factors, the short-term postoperative outcome in Fontan patients still remains variable.

Systemic Ventricular Diastolic Function

Systemic ventricular end-diastolic pressure has been shown to affect survival after the Fontan operation. Mair and colleagues¹² proposed a preoperative index of ventricular diastolic compliance, which incorporated end-diastolic pressure, as a means of predicting Fontan outcome in patients with tricuspid atresia. However, diastole is a complex process composed of different phases: aortic valve closure, followed by isovolumic ventricular relaxation and rapid pressure fall; ventricular relaxation continues through the mitral valve opening, generating suction forces that drive rapid early filling; early filling is then followed by diastasis (late filling) and, finally, atrial systole. The pressure immediately before mitral valve closure represents the single point where end-diastolic pressure is measured. Thus, it comprises only a small part of the continuum of diastole.

Fogel and associates¹³ used magnetic resonance blood tagging to study venous pathway flow in Fontan patients. These investigators showed that 70% of pulmonary blood flow is cardiac dependent and that the maximum velocity and flow occurred in late systole and early diastole. The lowest flow occurred during diastasis. This illustrates the limitation of using end-diastolic pressure alone to evaluate diastolic function in Fontan patients and emphasizes the importance of evaluating the period of early diastole.

The time course of the fall in isovolumic pressure of the systemic ventricle is thought to reflect the process of myocardial relaxation. This can be quantified by calculating the time constant of isovolumic relaxation (τ).¹⁴ In this technique, simultaneous measurements of pressure versus time are obtained at 5-ms intervals between aortic valve closure and mitral valve opening and the data points are fitted to an exponential function. In this way, abnormalities of the time course of ventricular pressure decay provide us with a measure of ventricular relaxation and, thus, early ventricular filling.

Preoperative Tau Versus Postoperative Outcome

The present study sought to explore the relationship between τ and short-term outcome in patients undergoing

Figure 2. Relationship between the time constant of isovolumic relaxation (τ) and length of hospital stay (log. base 10).

Fontan operation at a single institution. The study group represents a recent sample population who had all undergone prior palliative surgery. Intraoperative techniques remained constant during the time period. When logistic regression was used to look at predictors of pleural effusion greater than 10 days, none of the independent variables was significantly predictive. Multiple regression analysis of the preoperative independent variables demonstrated τ to be the only statistically significant predictor of length of ICU stay and total hospital stay. Therefore, τ was the most important predictor of postoperative short-term outcome in this group of patients undergoing the Fontan operation.

Of additional interest is the finding that the classic preoperative criteria of pulmonary vascular resistance and transpulmonary gradient, which were in acceptable range in all patients, failed to predict length of ICU or hospital stay, or outcome. In the current era of single ventricle management, it is infrequent to encounter patients with elevated pulmonary resistance presenting for Fontan, thus limiting the prognostic usefulness of these classic criteria for the majority of patients. In part this may be due to better and earlier palliation and staging, routine bidirectional Glenn as an interim stage, and earlier Fontan. Furthermore, many of the factors that previously affected the early postoperative course are either avoided or have better therapies available, such as avoidance of ischemic arrest, use of fenestrations, and agents such as phosphodiesterase inhibitors.

In this study the presence of a fenestration was not a significant predictor of length of ICU and hospital stay. There was a trend toward a higher incidence of prolonged pleural effusions in nonfenestrated versus fenestrated patients. However, as mentioned, the decision to fenestrate is often subjectively made in the operating room. The fact that fenestration did not influence ICU or hospital stay may represent a decreased effectiveness of a fenestration in the

face of impaired diastolic function, as fenestration shunting occurs primarily during diastole.

Limitations

Due to the retrospective nature of this study, tau was derived from ventricular pressure recordings obtained by fluid-filled catheters at the time of preoperative catheterization. The interposed fluid column can lead to lower natural frequencies and less optimal damping characteristics. Using a Bland-Altman plot in 10 patients, we demonstrated excellent correlation between fluid-filled catheter tau measurements and Millar catheter (Millar Instruments, Inc, Houston, Tex) measurements, with 9 of 10 measurements falling within 1 standard deviation of the mean. While the use of fluid-filled catheters may affect the absolute values of tau in the study patients, it should not affect the relative value between patients. Similar to its influence on calculations of systolic function such as dp/dt, heart rate may also influence tau. There did not appear to be significant heart rate variability at the time of catheterization, as strict sedation protocols were adhered to.

Clinical Relevance

Clearly, a single systemic ventricle has different properties compared with a biventricular heart,¹⁷ and a systemic left ventricle differs from a systemic right ventricle.^{18,19} Adults with single ventricles have been shown to have a significant risk for heart failure accompanied by high mortality.²⁰ However, objective quantification of single ventricular function can often be problematic. The present study highlights the importance of diastolic function and, more specifically, systemic ventricular relaxation in this important group of patients. In this study, tau was found to be predictive of length of ICU and hospital stay, whereas the classic criteria of pulmonary vascular resistance, transpulmonary gradient, and end-diastolic pressure were not. We have recently reported a correlation between preoperative tau and the risk of postoperative pancreatitis in Fontan patients.²¹ Although this represents a small study from a single institution, the predictive power of preoperative tau warrants continued investigation to determine whether it can be incorporated as a routine preoperative predictive value in the management of single ventricle patients.

Conclusions

In this study, preoperative systemic ventricular tau values significantly predicted length of ICU stay and total hospital stay in single ventricle patients undergoing the Fontan operation. Acceptable standard preoperative invasive indices did not ensure uncomplicated short-term outcomes. These preliminary data demonstrate the importance of systemic ventricular relaxation, even in those patients who are deemed to be at low risk by traditional preoperative criteria, and suggest that a more

comprehensive assessment of diastolic function is warranted during the pre-Fontan evaluation.

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