

Ventricular Diastolic Stiffness Predicts Perioperative Morbidity and Duration of Pleural Effusions After the Fontan Operation

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Background—We validated the clinical relevance of ventricular stiffness by examining surgical morbidity in children with univentricular hearts undergoing Fontan operation. We hypothesized that ventricular stiffness affects Fontan morbidity, particularly duration of pleural effusions.

Methods and Results—Sixteen children with right ventricular (RV) (n = 11) or left ventricular (LV) (n = 5) dominance were studied intraoperatively at a median age of 3.3 years (1.8 to 5.1). Transesophageal long-axis echocardiograms and ventricular pressure by micromanometer provided end-diastolic pressure (P) area (A) relations during initiation and conclusion of cardiopulmonary bypass. Curve fitting to the equation $P = \alpha e^{\beta A}$ defined the ventricular stiffness constant, β . Changes in β and clinical correlations were examined. Ventricular stiffness increased after bypass in patients with complete pre-bypass and post-bypass data (n = 11, $P = 0.023$, mixed models methodology). Pre-bypass β correlated well with duration of chest tube (CT) drainage ($r = 0.90$, n = 16), net perioperative fluid balance ($r = 0.71$, n = 14), and length of stay (LOS) ($r = 0.81$, n = 16). CT duration and LOS also correlated significantly with post-bypass β ($r = 0.77$ for both, n = 11), but insignificantly with preoperative catheterization pressures.

Conclusions—Intraoperative β predicts duration of CT drainage, net perioperative fluid balance, and LOS after the Fontan operation. These observations could improve risk stratification and clinical management of children at high-risk undergoing the Fontan operation. (*Circulation*. 2006;114[suppl I]:I-56–I-61.)

Key Words: diastole ■ Fontan procedure ■ hemodynamics ■ mechanics ■ morbidity

The Fontan operation, creation of a total cavopulmonary anastomosis such that pulmonary blood flow becomes passive rather than driven by a ventricular pump, is palliative surgery for patients with one functional ventricle. Originally developed for treatment of children with tricuspid atresia, it has evolved into the procedure of choice for all manner of complex cardiac lesions not amenable to biventricular repair. Despite surgical strategies to improve flow dynamics within the Fontan circuit, significant morbidities, including prolonged pleural effusions, arrhythmias, thromboembolic complications, and exercise intolerance, still complicate postoperative outcomes. Risk stratification and assessment of suitability for the Fontan procedure have been based on anatomic and hemodynamic variables.^{1–3} Risk stratification, however, remains imperfect. More thorough evaluation and understanding of ventricular performance in these patients are needed, including measurement of contractility and diastolic myocardial stiffness.

In vivo measurement of chamber properties and loading conditions in children with congenital heart disease may be

accomplished through pressure-area (P-A) analysis, using echocardiography and simultaneous ventricular pressure to approximate pressure-volume relations.^{4,5} In this study, we sought to define P-A relations at the time of the Fontan procedure and to correlate results with early postoperative outcomes, hoping to gain insight into optimization of perioperative management.

Previous studies of performance and efficiency of the single ventricle in the Fontan circulation have focused primarily on systolic function and ventricular-arterial coupling.^{6–8} Few studies have addressed myocardial stiffness, although the potential impact of ventricular diastolic properties on post-Fontan outcomes has been postulated. We hypothesized that ventricular stiffness affects the morbidity of Fontan surgery, particularly the duration of pleural effusions.

Methods

Patients

Sixteen children (Table 1) with right ventricular (RV) (n = 11) or left ventricular (LV) (n = 5) dominance were studied at a median age of

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TABLE 1. Characteristics of the Patients

Patient	Age (years) & Sex	BSA (m ²)	Diagnosis	Syndrome	Procedure	AVR	PA Distortion	EDP (mm Hg)	Mean PA (mm Hg)	β pre	β post	CT duration (days)	LOS (days)
1	3.6 M	0.62	AVC/RV	Heterotaxy	EX-Non	—	—	8	10	0.16	—	13	14
2	4.7 M	0.64	DORV	—	LT-Non	—	—	12	12	0.09	0.14	7	8
3	3.8 M	0.6	DORV	Heterotaxy	EX-Non	Mod	—	2	12	0.14	0.10	10	11
4	5.1 M	0.72	TA	Heterotaxy	EX-Non	—	—	11	13	0.09	—	11	13
5	3.2 M	0.61	HLHS	—	EX-Fen	Mild	No RUL PA	5	9	0.10	0.14	8	10
6	3.6 M	0.51	HLHS	—	LT-Fen	Mild	Small LPA	7	10	0.14	0.21	12	16
7	2.2 F	0.55	HLHS	—	LT-Fen	—	—	9	11	0.18	0.22	26	28
8	2.4 M	0.53	TA	—	LT-Non	—	—	7	8	0.12	0.15	10	12
9	3.1 M	0.63	HLHS	—	LT-Fen	—	Small LPA	8	13	0.11	0.15	6	10
10	2.7 M	0.51	AVC/RV	Heterotaxy	LT-Fen	—	—	9	12	0.20	0.22	24	49
11	3.3 F	0.6	HLHS	—	LT-Fen	—	—	7	13	0.35	0.23	34	41
12	4.1 M	0.64	AVC/LV	Heterotaxy	EX-Fen	Mild	—	8	12	0.19	—	23	36
13	1.8 F	0.42	AVC/RV	Tri 21	LT-Fen	Mod	—	10	12	0.10	0.08	10	11
14	2.5 M	0.63	HLHS	—	LT-Fen	Mild	Small LPA	8	12	0.10	—	7	8
15	2.2 F	0.5	PA/IVS	—	LT-Fen	Mild	Small RPA	13	12	0.14	—	6	7
16	3.3 F	0.62	TA	—	LT-Fen	—	—	8	11	0.11	0.13	10	13

AVC/LV indicates left ventricular dominant atrioventricular canal; AVC/RV, right ventricular dominant atrioventricular canal; AVR, atrioventricular valve regurgitation; BSA, body surface area; CT, chest tube; DORV, double outlet right ventricle; EDP, end-diastolic pressure at cardiac catheterization; EX-Fen, extracardiac fenestrated; EX-Non, extracardiac non-fenestrated; HLHS, hypoplastic left heart syndrome; LOS, length of stay; LPA, left pulmonary artery; LT-Fen, lateral tunnel fenestrated; LT-Non, lateral tunnel non-fenestrated; mod, moderate; Mean PA, mean pulmonary artery pressure at cardiac catheterization; PA/IVS, pulmonary atresia with intact ventricular septum; post, after cardiopulmonary bypass; pre, before cardiopulmonary bypass; TA, tricuspid atresia; Tri 21, trisomy 21; RPA, right pulmonary artery; RUL, right upper lobe.

3.3 years (1.8 to 5.1). Aortopulmonary collaterals were identified and coil-occluded during preoperative catheterization in 14. Patients 3 and 6 had no collaterals. Cavopulmonary anastomoses included 11 lateral tunnels (9 fenestrated) and 5 extracardiac conduits (2 fenestrated). All patients presenting for elective Fontan completion were considered for participation. None was excluded on the basis of age or cardiac diagnosis. Patients undergoing revision of previous total cavopulmonary anastomosis were excluded, as were patients with severe valvar insufficiency or moderate to severe systolic dysfunction. Informed consent was obtained from each patient’s legal guardian. This study was approved by the Institutional Review Board of the Columbia University Medical Center and performed in accordance with Good Clinical Practice guidelines. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Intraoperative Data Acquisition

All patients were anesthetized with sevoflurane and fentanyl. After heparinization and cannulation for cardiopulmonary bypass (CPB), a 5-Fr MPC500 micromanometer-tipped catheter (Millar Instruments, Houston, Tex) was inserted through a purse-string in the proximal ascending aorta and advanced into the ventricle. Ventricular pressure, systemic arterial pressure, and ECG were digitized at 200 Hz and transferred through a 16-channel analog to digital converter (MacLab ADInstruments Inc, Milford, Mass) to a computer (Powerbook G3; Apple Computers, Cupertino, Calif). Transesophageal long-axis echocardiograms of ventricular inflow at the level of the atrioventricular valve were obtained using a Sonos 5500 ultrasound system (Hewlett-Packard Co, Palo Alto, Calif), and recorded on videotape.

Pressure data and echocardiograms were recorded during the steady state immediately before (T1) and after (T4) CPB, and during ventricular emptying (T2) or filling (T3) on initiation and withdrawal of bypass. Figure 1 illustrates data collection during initiation of bypass in a patient with hypoplastic left heart syndrome. To facilitate correlation of beats, pressure and ECG data were superimposed on

echo recordings, and artifacts were added to the pressure channel (Figure 1). Intraoperative variables that could affect cardiac performance, including CPB time, cross-clamp time, fluid administration, and use of inotropic or vasoactive agents, were also recorded.

Data Analysis

Echocardiograms were planimetered on a VingMed CFM800 (GE Medical Systems, Chalfont St. Giles, United Kingdom). During steady states, minima in cyclic variation of mean arterial pressure identified beats at end-expiration for analysis. All beats during preload alteration at the initiation and conclusion of CPB were reviewed; beats were excluded for atrial or ventricular ectopy, poor echo quality, or artifacts on the pressure signal. End-diastole was identified on the echocardiograms as the frame immediately after AV valve closure in the late phase of ventricular filling. End-systolic area (ESA) was measured on the frame immediately before AV valve opening. End-diastolic area (EDA) and ESA were defined by planimetry of the ventricular endocardial borders (Figure 1) in accordance with American Society of Echocardiography standards. Areas were normalized by division by body surface area (BSA); BSA was derived from preoperative height and weight.

Correlation of EDA and end-diastolic pressure (EDP) required identification of corresponding beats using artifacts on the ventricular pressure tracing (Figure 1). Pressure was digitally differentiated. EDP was identified as the pressure preceding the rapid upstroke, determined from the rate of increase of ventricular pressure (dp/dt). EDP was plotted against EDA for calculation of diastolic indices. This process generally resulted in a data set of 10 to 15 beats for analysis at the initiation and conclusion of bypass.

Pre-bypass and post-bypass ventricular pressure, arterial pressure, and ECG were analyzed with custom routines developed in Matlab (The Mathworks Inc, Natick, Mass), including identification of EDP and mean ejection pressure.

Functional Indices

Diastolic function was assessed by P-A relations during preload alteration, fitting data to the equation $P = \alpha e^{\beta A}$, where P is ventricular

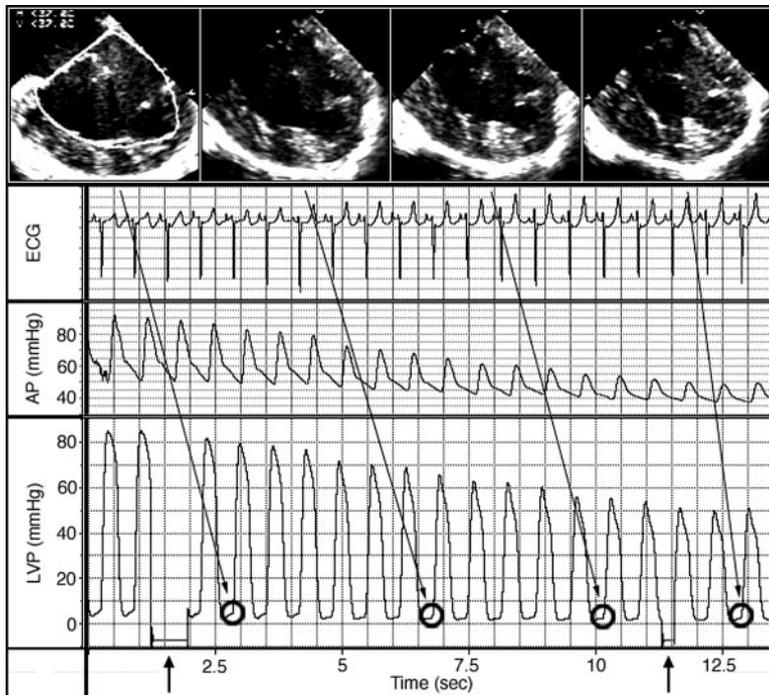


Figure 1. Raw data during initiation of bypass in patient 9. Shown top to bottom are: long-axis echocardiogram, ECG, systemic arterial pressure (AP), and ventricular pressure (LVP). Echo images correspond to end-diastolic points on the ventricular pressure tracing marked by circles. Arrows beneath the pressure tracing indicate artifacts inserted during data acquisition to facilitate off-line correlation of corresponding beats.

EDP, A is ventricular EDA, and α and β are curve-fitting constants. β is the ventricular stiffness constant, a measure of overall chamber stiffness. The correlation coefficient R^2 was defined for each curve to evaluate the goodness of fit. The minimal acceptable value was set at 0.7. All fits were acceptable, with values ranging from 0.73 to 0.99. β values were compared at the initiation and conclusion of bypass. Results for patients with dominant RV versus dominant LV were compared separately. Systolic function was quantified as preload recruitable stroke work (PRSW), the slope of the linear regression between stroke work (SW) and EDA: $SW = SA (MEP - EDP)$, where SA is stroke area and MEP is mean ejection pressure.

Clinical Outcome Measures

Patient charts were reviewed for chest tube (CT) duration, length of stay (LOS), and net perioperative fluid balance. CT removal was a clinical decision by physicians blinded to P-A data. Net perioperative fluid balance was calculated from the start of anesthesia to the end of the first 24 hours in the pediatric intensive care unit. Net fluid balance was defined as total intake minus total output determined from anesthesia records, CPB records, and flow sheets for the first 24 hours in the pediatric intensive care unit.

Statistical Analysis

Pre-bypass and post-bypass, as well as pre-bypass dominant RV and LV P-A, curves were modeled using a MIXED MODEL approach via the PROC MIXED procedure for repeated measurements. Slope estimates of pre-bypass and post-bypass were generated and compared.

Because repeated measurements within subjects may be correlated, the mixed modeling procedure allows modeling of a "correlation structure," or covariance pattern. This allows for improved estimates of the standard errors of measurement. The auto-regressive order one (ar1) structure, for correlations that are smaller for time points further apart, provided the best fit.

Multiple linear regression analysis determined any relationships between pre-bypass and post-bypass β , preoperative EDP, preoperative mean pulmonary artery pressure, preoperative oxygen saturation, and the 3 clinical outcome measures.

For all statistical analysis, data were analyzed using the SAS System software (SAS Institute, Inc, Cary, NC).

Results

Pre-bypass and post-bypass data were available in 11 patients. In 5 others, only pre-bypass data were usable because of problems with echo or pressure data ($n=4$) or arrhythmia ($n=1$). Post-bypass inotropic support was provided by dobutamine (3 to 6 mcg/kg per minute, $n=11$), milrinone (0.3 to 0.5 mcg/kg per minute, $n=3$), or milrinone (0.3 mcg/kg per minute) plus epinephrine (0.03 to 0.05 mcg/kg per minute) ($n=2$). All patients were in normal sinus rhythm pre-bypass. Post-bypass rhythm was sinus rhythm ($n=12$), atrially paced ($n=3$), or atrial bigeminy ($n=1$). Median CPB time was 118 minutes (range, 63 to 164 minutes). Median cross-clamp time was 38 minutes (range, 0 to 75 minutes). Four patients required circulatory arrest. Infectious complications included respiratory viruses (patients 4 and 6) and bacteriuria (patient 11, hospital day 37). No patient had postoperative phrenic nerve palsy.

Ventricular Properties

Post-bypass β increased to 0.14 (95% confidence limit [CL], 0.11, 0.17) from 0.11 (95% CL, 0.08, 0.14) pre-bypass ($P=0.023$, mixed models methodology). Average P-A curves are presented in Figure 2, and representative curves are presented in Figure 3. Pre-bypass β was not affected by RV ($n=11$) or LV ($n=5$) dominance (Table 2). PRSW did not change significantly post-bypass.

Clinical Correlations

Pre-bypass β correlated strongly with duration of CT drainage ($r=0.90$, $P<0.0001$) and LOS ($r=0.81$, $P=0.0002$) ($n=16$ for both) and net perioperative fluid balance ($r=0.73$; $P=0.003$, $n=14$) (Figure 4). CT duration and LOS also correlated with post-bypass β ($r=0.77$, $P=0.005$ for both; $n=11$). Maximum postoperative weight gain, expressed as a percent of preoperative weight, also correlated well with β ($r=0.64$) and CT duration ($r=0.74$) ($n=13$). Outcome measures did not correlate significantly with pre-bypass or post-bypass PRSW, or with EDP, mean pulmonary artery pressures, or baseline arterial oxygen saturations during preoperative catheterization.

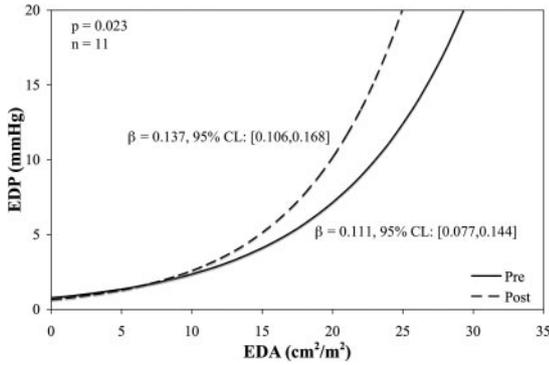


Figure 2. Average compliance curves pre- (solid line), and post- (dashed line) bypass. Group β values are presented.

Discussion

Our results indicate that ventricular stiffness can be measured during the Fontan procedure and that pre-bypass β correlates strongly with duration of pleural effusions, net perioperative fluid balance, and LOS. In addition, β increases after bypass, possibly reflecting myocardial edema. Contractility, measured as PRSW, was unchanged after Fontan surgery. Inotropic support was used postoperatively in all patients, however, confounding efforts to measure depression of systolic function. Effects of inotropes on contractility are believed to be more important than effects on diastolic function, particularly when edema is involved. This may explain why β was a useful predictor of outcome in this study, whereas PRSW was not.

Nevertheless, the balance of pharmacologic support and fluid administration after Fontan surgery is critical. Transient postcardiotomy myocardial depression is well-recognized, and inotropic support can also compensate for impaired diastolic function. Increased β reduces filling volume, and thereby cardiac output, at any given EDP. Although decreased preload can be overcome with fluid administration, this increases EDP and pulmonary and systemic venous pressures, particularly with a stiff ventricle. Extravasation of fluid is a likely result, enhancing the tendency to prolonged

TABLE 2. Characteristics of Patients With RV vs LV Dominance

	RV (n=11)	LV (n=5)	P
Age (years)	3.1±0.8	3.4±1.2	0.6
BSA (m ²)	0.57±0.07	0.61±0.09	0.4
EDP (mm Hg)	7.7±2.6	9.4±2.5	0.2
Mean PA (mm Hg)	11.4±1.3	11.2±1.9	0.8
β Pre-bypass	0.132	0.128	0.6
	95% CL, 0.116,0.149	95% CL, 0.106,0.149	

CL indicates confidence limit.
 β values were compared using Mixed Models methodology. All other values were compared by *t* test and are listed as mean±SD.

pleural effusions and other difficulties. Accordingly, the degree to which inotropic support and afterload reduction can be substituted for fluid administration, with secondary reductions in EDP, is key to the reduction of postoperative morbidity.

Ours is the first study to directly measure ventricular stiffness during preload alteration in single ventricle patients. Penny used Doppler echocardiography and micromanometer pressure during steady states pre-bypass and post-bypass to assess effects of Fontan surgery.⁹ They described the perioperative increase in mass-volume ratio of the single ventricle as an “acute hypertrophic cardiomyopathy” with inherent diastolic dysfunction, quantified as prolongation of the time constant of isovolumic pressure decay, tau (τ). Systolic function was preserved. Sandor defined diastolic function during pre-Fontan catheterization from pressure-volume points on individual heartbeats.¹⁰ Results in patients were supranormal compared with controls. More recently, Border measured tau (τ) at pre-Fontan catheterization and found correlation with LOS, but not with duration of effusions.¹¹

Previous echocardiographic studies are equivocal as to whether Fontan surgery impairs or augments diastolic function.¹²⁻¹⁴ Whereas the mass-to-volume ratio returns to preoperative values over 1 to 3 years postoperatively,^{12,15} diastolic dysfunction persists. Markers of impaired diastolic function have included prolonged isovolumic relaxation time, intra-

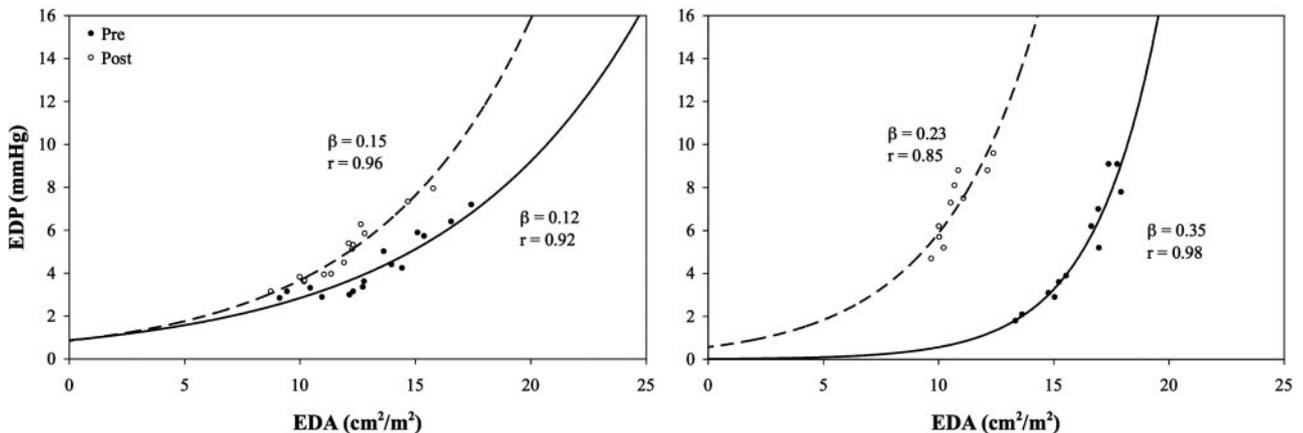


Figure 3. Individual compliance curves pre-bypass (solid lines) and post-bypass (dashed lines) for 2 patients with hypoplastic left heart syndrome: patient 9 (left) and patient 11 (right). These 2 patients had nearly identical filling pressures and mean pulmonary artery pressures on preoperative cardiac catheterization. Both underwent lateral tunnel Fontan with fenestration. Patient 9, whose pre-bypass β was 0.12, recovered uneventfully (CT duration=6 days; LOS=10 days). Patient 11, whose pre-bypass β was 0.35, had a prolonged recovery (CT duration=34 days; LOS=41 days).

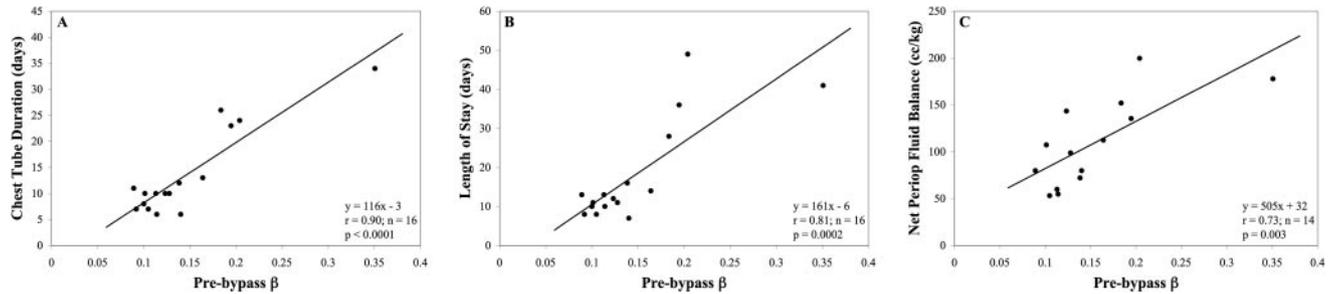


Figure 4. Correlation of chest tube duration (A), length of stay (B), and net perioperative fluid balance (C) with pre-bypass β .

cavitory flow during isovolumic relaxation, reduced early rapid filling, and abnormal wall motion during ventricular filling. Others describe the shift of diastolic filling to the later part of diastole as evidence of enhanced compliance.¹⁴

P-A analysis has been validated for assessment of LV and RV function, including use of long-axis RV images.^{16,17} P-A analysis during pre-Fontan cardiac catheterization, reducing preload with balloon occlusion of the inferior vena cava, could provide additional insights. Alternatively, Zile generated P-A curves from 3 diastolic coordinates on single beats during catheterization in adults with diastolic heart failure.¹⁸

Measurement of ventricular mass and mass/area ratio could enhance our study, but the echocardiographic sections used did not include the full epicardial border. Our previous studies of myocardial edema in the intact ventricle and isolated papillary muscle revealed linear correlations between diastolic properties, osmolarity of the coronary perfusates, and myocardial water content.^{19,20}

Limitations of our data include marginal control of variables affecting diastolic properties. Among these, heart rate did not change significantly after CPB; our data indicate minor effects of heart rate variability on diastolic properties.²¹ A limited and inconsistent range of EDP for our patients limited comparisons across the group and dictated use of a simple exponential equation for curve-fitting. Our study is also not large enough to identify differences among subgroups (dominant ventricle, specific diagnoses, etc), or to perform multivariate analysis incorporating other potential risk factors for prolonged pleural effusions.²²

Our results argue for continued focus on diastolic function and strategies targeting compliance and perioperative fluid balance in single ventricle patients. Pharmacologic agents that might enhance compliance include phosphodiesterase inhibitors, spironolactone, and levosimendan. Alternatively, inotropes and/or multi-site pacing can augment contractility and ventricular efficiency, allowing the ventricle to maintain cardiac output at a lower EDP. Finally, strategies for perioperative fluid management include modified ultrafiltration and aggressive diuresis, as set out by Cava.²³ Additional advancements could include real-time computerized P-A analysis and development of preoperative predictors of intraoperative diastolic properties, including magnetic resonance imaging and genetic markers.

Conclusions

Quantification of diastolic properties during Fontan surgery demonstrates an increase in the ventricular stiffness constant,

β , after cardiopulmonary bypass. Furthermore, β appears to predict perioperative surgical morbidity. These observations may aid risk stratification and lead to improved clinical management.

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Disclosures

None.

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