Characterization of Left Ventricular Dysfunction by Myocardial Strain in Critical Pulmonary Stenosis and Pulmonary Atresia After Neonatal Pulmonary Valve Balloon Dilation

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Transient left ventricular (LV) dysfunction occurs in some infants born with critical pulmonary stenosis (PS) or membranous pulmonary atresia with intact ventricular septum (PAIVS) after pulmonary valve (PV) balloon dilation (BD). The cause for this is not well understood. We sought to characterize this LV dysfunction by investigating regional differences in this cohort using myocardial strain imaging. Patients who underwent neonatal (<2 weeks age) PV BD for critical PS or PAIVS from Jan, 2007 to March, 2014 with echocardiographic images suitable for strain analysis were identified; infants with ≥moderate post-BD LV dysfunction (ejection fraction <40%, n = 8) were matched 1:1 with controls who underwent PV BD but did not develop LV dysfunction. Longitudinal and circumferential global and segmental strain were analyzed before and after PV BD. For the 8 LV dysfunction cases, LV global longitudinal strain worsened after PV BD (−16% pre- vs −8% post-PV BD, p = 0.008) with similar impairment in global LV circumferential strain (−17% vs −8%, p = 0.008); there was no significant change in RV global or segmental longitudinal strain pre- vs post-PVBD. No significant pre/post-BD differences in global or circumferential strain were found in control pts. Segmental analysis of longitudinal and circumferential LV strain before and after balloon dilation in cases demonstrated decreased strain in all segments, but more pronounced and statistically significant in septal segments as compared with the free wall. In conclusion, transient LV dysfunction post-PV BD for critical PS/PAIVS is characterized by impaired global longitudinal and circumferential LV strain, with the most significant reductions in strain at the interventricular septum; longitudinal RV strain remains unchanged. These findings suggest that the mechanism of LV dysfunction post-PV BD is adverse ventricular-ventricular interactions specifically involving the interventricular septum. **(Am J Cardiol 2019;123:454−459)**

Patients with congenital critical pulmonary stenosis (PS) and membranous pulmonary atresia with intact ventricular septum (PAIVS) typically undergo transcatheter intervention in the neonatal period with pulmonary valve balloon dilation (PVBD) with or without previous pulmonary valve perforation.[1−4] Before right ventricular (RV) decompression, these conditions are characterized by severely increased RV afterload. A previous study from our institution demonstrated that a significant group (20%) of these patients develop transient left ventricular (LV) dysfunction following transcatheter relief of RV outflow tract obstruction.[5] LV dysfunction before relief of neonatal RV outflow obstruction has also been described in the literature.[6,7] In addition, regional LV dysfunction has been described in patients with mild coronary abnormalities. Risk factors for the development of LV dysfunction in our previous study included those with larger tricuspid and pulmonary valves, and larger apical RV areas. This observation suggested that transient post-PVBD LV dysfunction might be related to negative ventricular−ventricular interactions in the setting of larger right ventricles. Deformation (myocardial strain) imaging allows for the direct interrogation of myocardial performance, including global and segmental analysis.[8] We hypothesized that due to adverse ventricular−ventricular interaction, those who developed LV dysfunction following PVBD would demonstrate more significant impairment of septal strain than in other LV segments. We sought to characterize changes in RV and LV function by strain imaging before and following PVBD in a cohort of PS/PAIVS patients who developed moderate or worse LV dysfunction after this procedure.

Methods

Included infants had the diagnosis of either critical PS (requiring prostaglandin infusion) or membranous PAIVS

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and underwent catheter-based intervention on the PV from January 2007 through March 2014. Those older than 2 weeks at intervention, and those with RV-dependent coronary circulation by angiography were excluded from the study. In addition, patients whose echocardiograms were not suitable for strain analysis were excluded. Within this cohort, infants with moderate-severe LV dysfunction (ejection fraction <40% by 5/6 area × length measurement performed on 2-dimensional echocardiogram) after PVBD were identified and matched 1:1 with infants who did not develop LV dysfunction after PVBD (EF > 54%). Matching was performed on the underlying anatomic diagnosis (PS vs PAIVS) as well as weight at the time of the procedure (within 500 g).

Echocardiograms were performed using the IE33 (Phillips Medical Systems, Andover, Massachusetts) machines using the S12, S8, or S5 probes. All patients had a detailed precatheterization echocardiogram performed and at least 1 postcatheterization echocardiogram within 14 days of the procedure. For those with multiple postcatheterization echocardiograms before discharge, the study with the lowest LV ejection fraction was analyzed.

Variables and z-scores collected for analysis from preprocedure echocardiograms included PV annulus dimension, main pulmonary artery dimension, tricuspid valve annulus (lateral and antero−posterior dimensions), tricuspid valve area, RV diastolic apical area from 4-chamber view,[9] LV end diastolic and end systolic dimensions (2D measurements), and LV end diastolic and end systolic volumes (using the 5/6×Area×length algorithm)[10] and ejection fraction. Z-scores were calculated as previously described.[11]

A commercial speckle tracking-based analysis software (2D CPA version 1.1.3, TomTec imaging systems, Unterschleissheim, Germany) was used to measure global endocardial peak systolic longitudinal strain (GLS) for the LV and the RV from the apical 4 chamber views, and global endocardial peak systolic circumferential strain (GCS) from a parasternal short-axis view at the mid ventricular level for the left ventricle. The software automatically tracked the endocardial border for a single cardiac cycle after initial manual tracing performed at end systole, with manual adjustments performed by a single investigator (CR) to achieve adequate tracking as assessed by visual inspection; subjects were excluded from analysis if tracking was judged to be inadequate secondary to poor image quality. Measured systolic deformation parameters included global peak circumferential strain (GCS, %), and global peak longitudinal strain (GLS, %), segmental values were recorded for the left ventricle; the septum was devoted to the LV and the RV strain analysis was limited to the lateral apex, mid, and basal wall.

Hemodynamic and echo data are expressed as mean ± SD. Continuous variables were compared using the Wilcoxon rank sum test or unpaired *t* test, and categorical variables using Fisher's exact test. For both patients and controls, LV and RV strain before and after PVBD were compared using the Wilcoxon signed-rank test.

This retrospective study was performed according to a protocol approved by the Committee for Clinical Investigation at Boston Children's Hospital.

Results

Eight infants who developed at least moderate LV dysfunction after PVBD met all other inclusion criteria as defined above. Pertinent data for these patients and their matched controls are shown in Table 1. The indications for PVBD were standard indications for neonates with critical PS or PAIVS: all patients with pulmonary stenosis were on prostaglandin to maintain ductal patency and all patients with PAIVS had right ventricular dependent coronary circulation excluded. Post-PVBD LV dysfunction patients and controls were well matched in terms of diagnosis, age, gender, and size. The patients that developed significant LV dysfunction after PVBD had larger tricuspid valve z-scores on their precatheterization echocardiograms (1.73 vs −1.37, $p = 0.001$). In addition, at catheterization the LV dysfunction patients had lower absolute RV pressure (71 mm Hg vs 109 mm Hg, $p = 0.01$), and lower postdilation right ventricular to systemic pressure ratios (0.7 vs 1.12, $p = 0.04$).

For the 8 control patients, there was no significant change in the LV global peak longitudinal strain (−15.8 vs. −14.4 $p = 0.95$) or the global peak circumferential strain (−18.9 vs −17.2 $p = 0.95$) pre- versus post-PVBD. In addition, there was no significant change in RV global peak longitudinal strain (with analysis limited to the RV lateral wall) pre- versus postintervention (−15.4 vs −16.4, $p = 0.56$). In the 8 LV dysfunction patients, there was a significant deterioration in LV global peak longitudinal strain (−16.4 vs −8.4, $p = 0.008$), with a similar deterioration in global peak LV circumferential strain (−17.2 vs −8.4, $p = 0.008$). There was no significant change in RV global peak longitudinal strain (−19.7 vs −13.2, $p = 0.74$) for the LV dysfunction patients. There was, as expected a significant difference when comparing the change pre- and post-PVBD in global longitudinal strain between the LV dysfunction patients and the control patients (7.7 vs −1.4, $p = 0.005$). The same difference was observed when comparing global LV circumferential strain pre- and post-PVBD between LV dysfunction patients and control patients (8.1 vs −0.2, $p = 0.01$).

The results of LV longitudinal segmental analysis of strain imaging for LV dysfunction patients and controls pre- and post-PVBD are depicted in Figures 1A and 1B. Segmental analysis of RV segmental longitudinal strain (limited to the lateral wall of the right ventricle) demonstrated no significant change pre- versus post-PVBD (Figures 2A and 2B). Segmental analysis of both the longitudinal and circumferential LV strain in the patients with LV dysfunction demonstrated a reduction in strain in all segments evaluated, but most pronounced and statistically significant in the septal segments as compared with the free wall (Figure 3).

Discussion

The aim of this study was to investigate whether the development of post-PVBD left ventricular dysfunction was at all related to a change in the myocardial strain of the interventricular septum after relief of right ventricular outflow tract obstruction. We hypothesized that the patients

Table 1
Pertinent patient and control characteristics for patients who developed left ventricular dysfunction postpulmonary valve balloon dilation

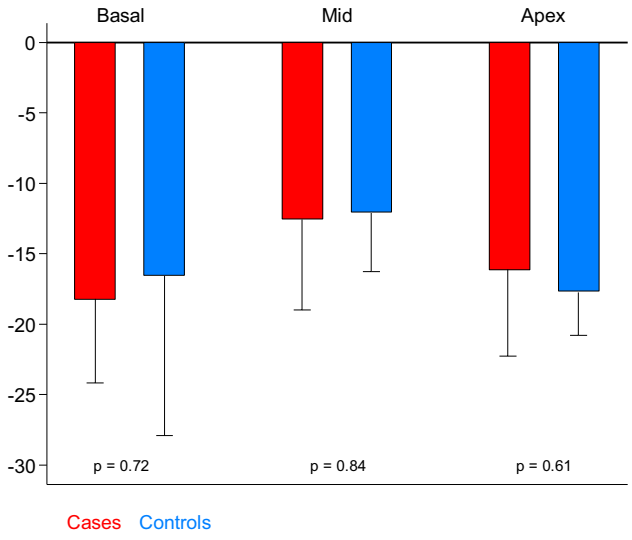
Patient (A)/ Control (B)	Age at cath (days)	Dx	Gender	Weight (kg)	Precath LV EF (%)	RV apical area (cm^2)	TV AP (z-score)	Predilation RVp (mm Hg)	Postdilation RVp (mm Hg)	Postcath LV EF (%)
1A	3	PS	F	2.8	64	2.64	1.01	37	36	12
1B	1	PS	M	2.6	59	2.61	−1.09	130	98	61
2A	0	PS	M	2	50	1.76	1.57	70	40	38
2B	2	PS	M	2.5	59	1.47	−1.92	102	40	55
3A	12	PS	M	3.2	56	4.26	4.72	56	45	37
3B	1	PS	F	3.5	55	3.6	−0.39	120	57	65
4A	1	PA	M	3.2	46	4.14	3.99	74	43	32
4B	1	PA	F	3	54	0.84	−2.5	112	50	58
5A	1	PS	F	3.3	54	2.67	−1.17	97	50	36
5B	1	PS	M	3.9	58	2.01	−1.5	110	68	54
6A	2	PA	M	3.3	64	1.25	−3.96	108	47	30
6B	0	PA	M	3.2	55	1.87	−0.98	150	90	55
7A	4	PS	F	3.2	52	2.2	0.5	62	48	28
7B	1	PS	M	3.2	60	3.93	0.22	79	39	64
8A	2	PA	F	3.4	59	2.81	0.78	106	41	31
8B	3	PA	F	3.7	69	2.22	−2.1	109	114	54

Abbreviations: AP = anterior-posterior; Cath = cardiac catheterization; EF = ejection fraction; F = female; Dx = diagnosis; M = male; LV = left ventricle; PA = pulmonary atresia; PS = pulmonary stenosis; RV = right ventricle; RVp = right ventricular pressure; TV = tricuspid valve.

who developed LV dysfunction after PVBD had larger right ventricles and therefore an increased propensity for negative ventricular-ventricular interactions. Our previous study demonstrated that for those patients who developed LV dysfunction, normalization of ventricular function occurred in a relatively short period of time (median 10 days in that study), consistent with a temporary alteration in ventricular-ventricular interaction. The results of this study utilizing strain imaging demonstrate that following PVBD, patients with at least moderately decreased LV ejection fraction had a deterioration in both longitudinal and circumferential global strain, with the most significant impairments in strain occurring at the interventricular septum.

Our results support the theory that the mechanism for LV dysfunction post-PVBD involves negative ventricular-ventricular interactions given that the interventricular septum was the most significantly affected after PVBD. More specifically, the mechanism of altered ventricular performance under these circumstances is at least in part attributable to altered myocardial performance in the ventricular septum and not simply to changes in ventricular configuration following relief of severe right ventricular outflow tract obstruction. In addition, the group that developed LV dysfunction after PVBD had lower pre- and postcardiac catheterization right ventricular pressure to systemic pressure ratios which may suggest that a relatively hypertensive right ventricle assists with the LV ejection fraction both pre- and post-PVBD. The end diastolic volumes of the LV post-PV BD were not significantly different between the 2 groups, indicating that the onset of LV dysfunction was unlikely to be secondary to an acute change in volume loading of the LV in the absence of a patent ductus arteriosus.

Adverse changes in myocardial strain in 1 ventricle due to pressure unloading of the other ventricle has been reported in other settings. Right ventricular myocardial strain following relief of aortic stenosis has been examined to see the effects of LV afterload on RV myocardial performance, and 1 group demonstrated that RV midwall longitudinal strain was improved following aortic balloon valvuloplasty, however, patients with the highest RV strain at baseline experienced deterioration in strain post-aortic valve dilation.[12] In addition, in patients with pulmonary hypertension studies have demonstrated that LV myocardial strain is most altered within the septum, and that septal strain progressively worsens as pulmonary hypertension increases as measured by invasive hemodynamics.[13] One theory of interventricular interaction is that it relates to changes in ventricular geometry secondary to altered septal geometry, and it is the change in geometry that induces a change in ejection fraction.[14] The tetralogy of Fallot literature reports improvements in global LV strain following pulmonary valve replacement,[15,16] with the data showing that the larger the RV is prior to pulmonary valve replacement the LV is negatively affected due to the altered interventricular septal geometry. A recent study demonstrated that there is some late impairment in LV mechanics, as measured by a lower circumferential strain rate and lower ejection fraction following PVBD for isolated pulmonary stenosis as children,[17] which suggests that long-term follow-up of these patients for altered RV-LV interactions might be beneficial. Moreover, given



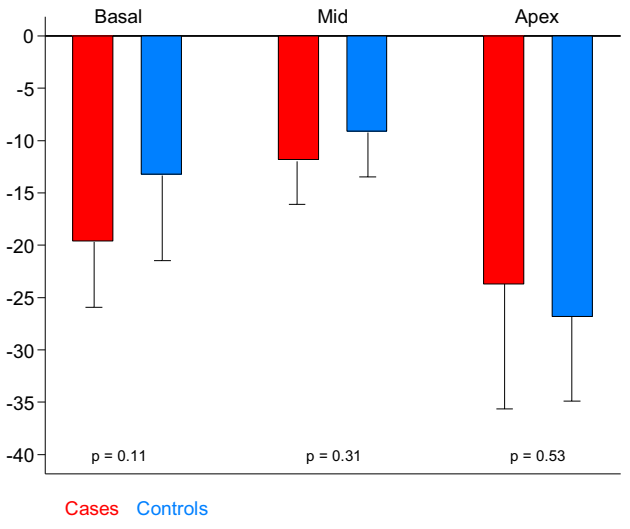
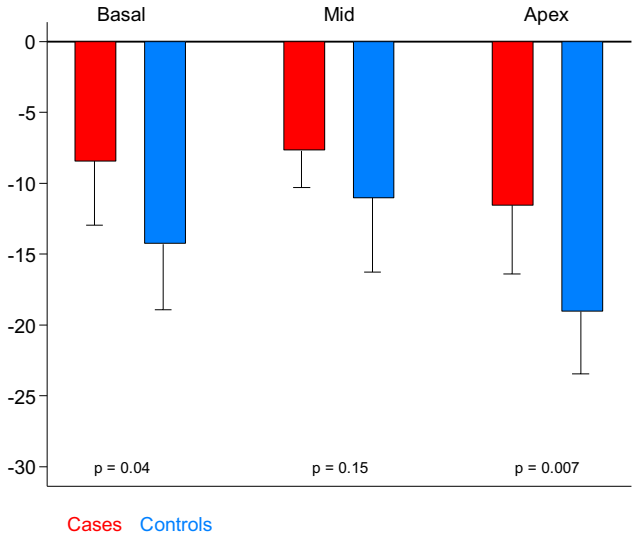


Figure 1A. Segmental analysis of left ventricular strain imaging prepulmonary valve balloon dilation (lateral wall and septum).



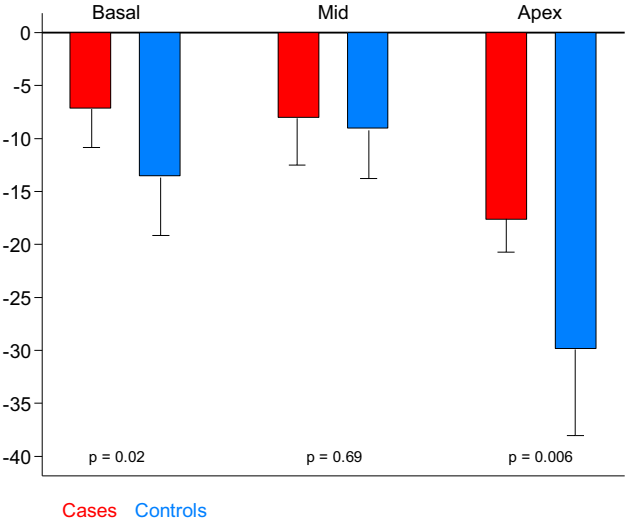


Figure 1B. Segmental analysis of left ventricular strain imaging postpulmonary valve balloon dilation (lateral wall and septum).

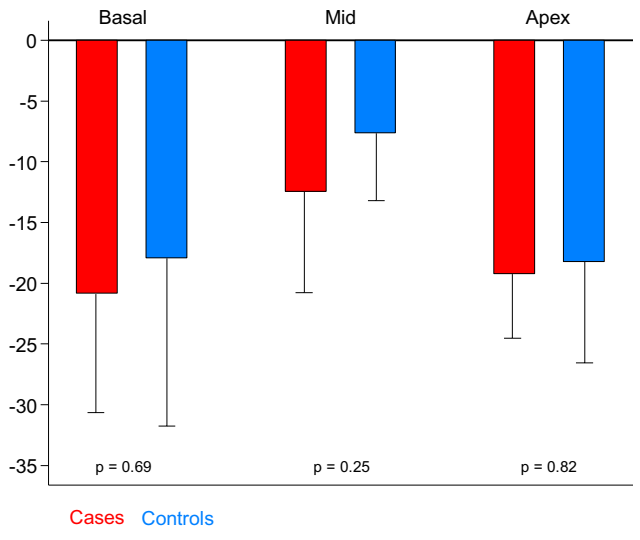


Figure 2A. Segmental analysis of right ventricular longitudinal strain pre-pulmonary valve balloon dilation.

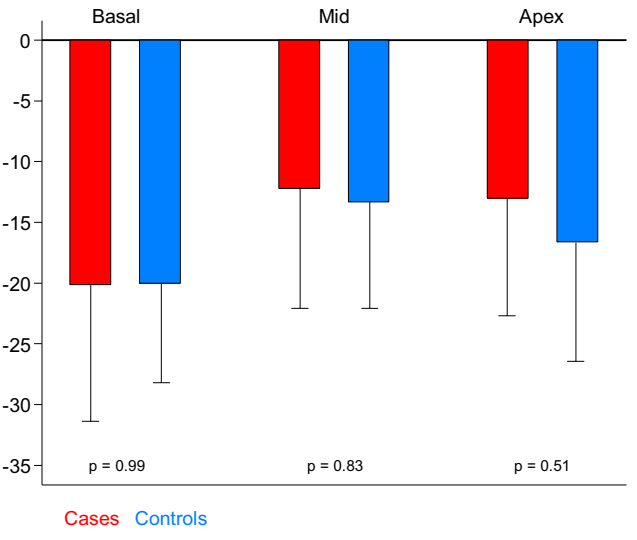


Figure 2B. Segmental analysis of right ventricular longitudinal strain post-pulmonary valve balloon dilation.

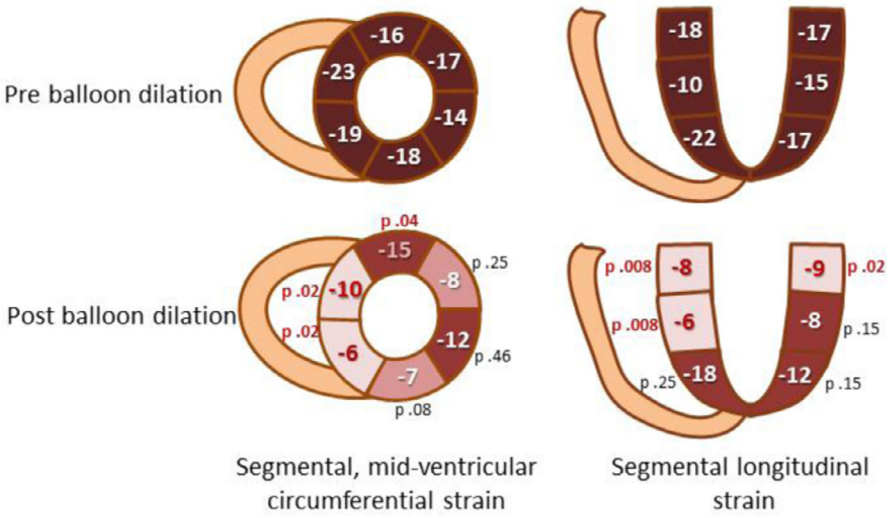


Figure 3. Segmental left ventricular strain before and following pulmonary valve balloon dilation in lv dysfunction patients. The greatest impairment in strain was seen in segments of the ventricular septum.

that all of the patients in the study had recovery of their LV systolic function it is plausible that the observed decrease in strain is due to altered conditions rather than acute myocardial injury.

This study has several limitations that stem primarily from the retrospective study design. Most importantly, none of the echocardiographic images were acquired specifically for the purpose of strain analysis and therefore were not optimized for that purpose. Strain analysis was performed on stored images with a frame rate of $\leq$ 30 frames/s which could underestimate peak strain velocities. However, the strain analysis for pre- and post-PVBD used the same frame rate so comparison is reasonable between these 2 groups. The echocardiographic surveillance for LV dysfunction post-PVBD was not standardized. In addition, myocardial strain is influenced by multiple factors including heart rate, preload, and afterload which were not controlled for in our study. Moreover, we looked at the right ventricular strain on the echocardiogram that demonstrated the worst left ventricular function.

In conclusion, transient LV dysfunction post-PV BD for critical PS/PAIVS is characterized by impaired global longitudinal and circumferential LV strain, with the most significant reductions in strain at the interventricular septum; longitudinal RV strain remains unchanged. These findings suggest that the mechanism of LV dysfunction post-PV BD is adverse ventricular−ventricular interactions specifically involving the interventricular septum.

Disclosures

The authors have no conflicts of interest to disclose.

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