Progressive changes in residual gradient after aortic coarctation repair and its role in the prediction of reintervention: A longitudinal data analysis

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ABSTRACT

Background : **Repair of aortic coarctation through left thoracotomy is the standard treatment when anatomically feasible. Long-term outcomes are well studied, including the need for reintervention. However, the timely variation in residual gradients across the repaired segment is ill-defined. The aim of this work was to study the progressive changes of estimated peak gradient (ePG) acquired by transthoracic continuous-wave Doppler echocardiography across the aortic arch after repair and to assess the role of timing of assessment and values of ePG in prediction of reintervention.**

Materials and Methods : **All eligible patients for this study who underwent aortic coarctation repair through left thoracotomy from 2001 to 2017 were reviewed. Details of the aortic arch dimensions and associated lesions were obtained by transthoracic echocardiography (TTE). The primary outcome was the ePG across the aortic arch after repair. Longitudinal data analyses with mixed effect modeling were used to determine independent predictors for ePGs.**

Results : **A total of 312 patients were included. Median age and weight were 30 days and 4 kg, respectively. Associated lesions included ventricular septal defect (VSD) (53%), bicuspid aortic valve (53%) and mitral stenosis (25%). Over 15-years follow-up the freedom from reintervention was 92.3%, while 24 out of the 312 patients underwent reintervention (7.7%). Longitudinal data analyses of serial 2566 TTE studies were done. The graphical display showed that the ePG across coarctation area in the first postoperative TTE was the most notable difference between those who underwent reintervention and those who did not. Further testing with proportional hazard and logistic regression modeling confirmed this finding. The area under receiver operating curve statistics showed that an ePG of 25 mmHg is an optimal cutoff value for the prediction of the reintervention.**

Conclusions : **The ePG acquired in the first postoperative TTE is the most important predictor for reinterventions. The presence of VSD is associated with decreased ePGs. We propose that an ePG in the first postoperative TTE of 25 mmHg or more is a strong predictor for the need of reintervention.**

Keywords : Aortic arch, coarctation, congenital heart surgery, thoracotomy

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INTRODUCTION

Aortic coarctation is a common congenital heart disease either in isolation or as a part of more complex congenital cardiac anomalies.[1] The general presentation is variable from mild symptoms to a clinical state of shock. However, the clinical presentation in the newborn period is critical as it may present with decreased oral intake, shortness of breath, and lethargy and progress to obvious Congestive heart failure (CHF) and shock.[2] The standard treatment of aortic coarctation in neonates and infants is surgical through thoracotomy when this is anatomically feasible (that is if transverse aortic arch diameter >3 mm in neonates).[3] More complex aortic arch anatomy or the presence of associated defects that require concomitant repair entails a median sternotomy approach.

The goal of surgical repair is to eliminate the pressure gradient across the aortic arch (clinical blood pressure gradient between the upper and lower limbs) which is further delineated by transthoracic echocardiography (TTE) using continuous-wave (cw) Doppler to estimate pressure gradients noninvasively. Although most patients who have hypertension before surgery need at least temporary medical treatment after surgery, it appears that releasing the aortic arch obstruction promptly rather than trying to treat hypertension with antihypertensive medications is better.[4] Suboptimal repair would result in increasing pressure gradients and a need for reintervention. Predictors for reintervention have been studied previously and some of these variables include small weight and hypoplastic transverse aortic arch.[5]

The estimated peak gradient (ePG) by transthoracic cw-Doppler echocardiography across the aortic arch after repair has been the most important determinant variable for reinterventions. Because the ePG can vary with somatic growth or the presence of other lesions such as a ventricular septal defect (VSD), we sought to examine the behavior of these gradient measurements and to determine their relationship with the need for a reintervention to guide clinical decision making.[6]

This study focused on and presents only outcome data for surgical repair through left thoracotomy, which is our institutional repair strategy for aortic coarctation.

MATERIALS AND METHODS

Study population

After approval of research ethics board, all consecutive pediatric cardiac surgery patients (age <14) who underwent primary repair of aortic coarctation through left thoracotomy between 2001 and 2017 were reviewed. Single ventricular physiology patients were excluded.

Surgical techniques and echocardiographic measurements

Our institutional repair strategy for aortic coarctation is through left thoracotomy when anatomically feasible (that is, if the dimension of the aortic arch distal to the innominate artery is at least 1 mm/kg). With this approach, the patent ductus arteriosus (PDA) is ligated and divided and the aortic arch is repaired by varying techniques of end-to-end or extended end-to-end technique.

TTE was used for all assessments that included all parts of the arch: Proximal arch (between innominate artery and left common carotid artery), distal arch (between left common carotid and left subclavian artery), the distance between left subclavian artery and the isthmus area with z-scores for all these measurements. Further, TTE was also used to evaluate associated defects, including VSD, mitral stenosis (MS), presence and size of PDA, bicuspid aortic valve (BAV), aortic valve annulus z-score and ePG across aortic valve). During serial follow-up visits TTE was repeated in all patients 1) to measure ePGs across the aortic arch and 2) to determine the presence of a "diastolic run-off" in the abdominal aorta to evaluate the presence of a recoarctation of the aorta or not. The first TTE after surgery was defined as the echocardiography study before discharge.

Primary outcome

The primary outcome was the ePG across the aortic arch measured by cw-Doppler echocardiography. Secondary outcome included assessment of the role of timing of assessment and values of ePG in prediction of reintervention by aortic balloon angioplasty.

Statistics

Continuous data were presented as means with standard deviation or medians with ranges and categorical data were presented as proportions. Kaplan–Meier statistics were used to display time to reintervention. A multivariable proportional hazard modeling was used to identify the influence of preoperative and postoperative variables on the need for reintervention. Longitudinal data analyses with mixed effect modeling was used to display and identify predictors of the progressive changes in the ePGs after repair. The statistical analysis system (SAS), developed by SAS institute, version 9.4, Cary, USA was used for all statistical analyses.

RESULTS

Baseline characteristics of the entire cohort

Three-hundred and twelve patients were included. Median age was 1 months (0.1–144). One hundred sixty-four (53%) had associated VSD, 77 (25%) had MS and 164 (53%) had associated BAV. There was no in-hospital mortality. Twenty-four (7.7%) patients underwent reintervention by means of balloon angioplasty [Tables 1 and 2].

Comparison based on reintervention and preoperative variables

Univariable comparison between those who did not undergo reintervention and those who did showed no differences based on preoperative variables with the exception of the diameter of the aortic valve annulus and the ascending aorta [Tables 3 and 4].

Comparison based on reintervention and surgeon

There were three surgeons coded as surgeon A through C. There was no significant difference in the rate of reintervention between different surgeons [Table 5].

Time to reintervention analysis

Time to reintervention using Kaplan–Meier statistics for the entire cohort of 312 patients showed 24 events (reintervention) with a freedom of reintervention along the span of the study of 25-years was 92.3%. The median follow-up time was 6.2 years [Figure 1] survival analysis with stratification by the surgeon, VSD, PDA, MS, BAV, and diastolic run off using log-rank statistics showed no significant differences. Proportional hazard modeling for all variables with time-to-reintervention as an outcome with stepwise selection methodology showed that the only predictive preoperative variable for reintervention was the dimension of the ascending aorta ($P = 0.02$). Further analysis with the area under receiver operating characteristics curve showed that an ascending aortic diameter of <5.5 mm is a predictor for reintervention with a hazard ratio of 4.

Serial echocardiographic measurements

All patients underwent serial TTE evaluations. The minimum number of TTE done per patient was 2 and the max was 27 (mean = 7.4 ± 4.8), as shown in [Figure 2].

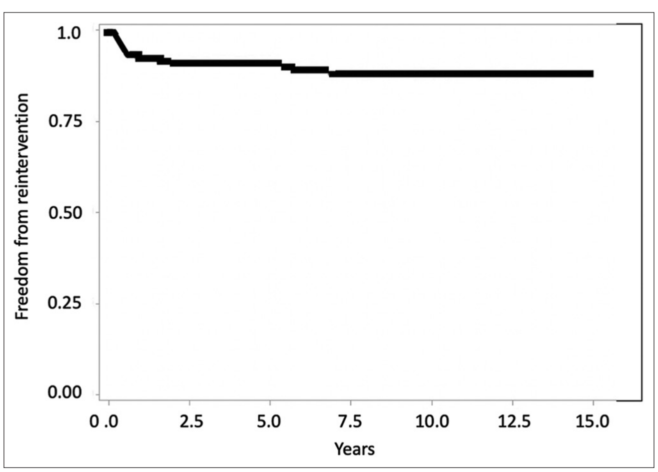

Figure 1: Kaplan–Meier curve for time to reintervention of the entire cohort of patients showing 24 events (reintervention) with a freedom of reintervention along the span of the study of 15-years

Time to reintervention in the reintervention group (*N* = 24)

Of the 24 patients who underwent reintervention, 18 patients (75%) underwent the reintervention within 1 year following the surgery [Figure 3].

Longitudinal data analysis

All serial TTE studies ($N = 2566$) for all patients were included. Longitudinal data graphical data display were used respecting the different timing of the TTE measurements. The averaged longitudinal data for the ePG showed that most of the changes happen in the 1st 300 days following surgery [Figures 4 and 5].

Longitudinal data analysis with stratification

Stratification by the presence of BAV, MS, and surgeon did not show any significant differences. Stratification by VSD showed reduced ePGs as physiologically expected [Figure 6].

The stratified longitudinal data display demonstrated the rate of drop of ePGs between those who underwent reintervention and those who did not [Figure 7]. Longitudinal data analysis with mixed effect modeling confirmed these findings in graphical display. The significant variables in relation to the ePGs following aortic coarctation repair included: The presence of PDA and VSD (both were significantly associated with lower ePGs, $P < 0.05$). The presence of diastolic run-off was significantly associated with higher ePGs ($P < 0.05$).

Table 1: General characteristics of all patients with coarctation of the aorta and their associated cardiac lesions (*n*=312)

Variable	Proportion, *n* (%)
VSD	164 (53)
PDA	184 (59)
BAV	164 (53)
MS	77 (25)

BAV: Bicuspid aortic valve, MS: Mitral stenosis, PDA: Patent ductus arteriosus, VSD: Ventricular septal defect

Table 2: Mean values of the general characteristics, aortic dimensions and pressure estimations by continuous-wave-Doppler echocardiography of the entire cohort of patients (*n*=312)

Variables*	Mean±SD
Age (day), median	30.5
Weight (kg)	4.2±3.2
Estimated aortic valve peak gradient (mmHg)	9.6±11
Aortic valve annulus diameter (mm)	6.6±1.9
Ascending aortic diameter (mm)	7.6±2.1
Transverse aortic diameter between innominate and left common carotid arteries (mm)	4.8±1.5
Transverse aortic diameter between left common carotid and left subclavian arteries (mm)	3.9±1.3
Length of aortic isthmus (mm)	9.1±3.9
ePG of descending aorta (mmHg)	37.0±21.6

*All variables were measured preoperatively. SD: Standard deviation, ePG: Estimated peak gradient

As the rate of drop of ePGs immediately after surgery was the most notable difference between patients based on reintervention, further testing with proportional hazard modeling with the first ePG after surgery as a predictor and all variables with stepwise selection was done.

The ePG in the first postoperative TTE was the only predictor for reintervention with a hazard ratio of 1.1 ($P < 0.0001$). The best cut of value for prediction of reintervention based on the ePG obtained from the first postoperative TTE was determined from the proportional

Table 3: Univariable analysis of reintervention versus no intervention in all patients by comparison of general characteristics, aortic dimensions and and pressure estimations by continuous-wave-Doppler echocardiography

Variables	No intervention (*n*=288)	Intervention (*n*=24)	*P*
Age (day)	168±514	147±554	0.8
Weight (kg)	4.3±3.3	3.3±2.4	0.08
Estimated aortic valve peak gradient (mmHg)	9.7±11.3	8.4±7	0.4
Aortic valve annulus diameter (mm)	6.7±6.4	5.9±5.4	0.01
Ascending aortic diameter (mm)	7.7±7.4	6.7±6.1	0.007
Transverse aortic diameter between innominate and left common carotid arteries (mm)	4.8±1.6	4.5±1.3	0.2
Transverse aortic diameter between left common carotid and left subclavian arteries (mm)	3.9±1.3	3.5±1	0.07
Length of aortic isthmus (mm)	9.2±3.9	8.7±4.1	0.6
ePG of descending aorta (mmHg)	36.8±21.5	38.9±23.5	0.6

ePG: Estimated peak gradient

Table 4: Univariable analysis of reintervention versus no intervention in all patients by comparison of associated congenital heart lesions

Variable	No intervention (*n*=288), *n* (%)	Intervention (*n*=24), *n* (%)	*P*
VSD	149 (52)	15 (63)	0.3
PDA	168 (58)	16 (67)	0.4
BAV	150 (52)	14 (58)	0.5
MS	72 (25)	5 (20)	0.6

BAV: Bicuspid aortic valve, MS: Mitral stenosis, PDA: Patent ductus arteriosus, VSD: Ventricular septal defect

Table 5: Univariable analysis of reintervention versus no intervention in all patients by comparison of involved surgeons

Surgeons	No intervention, *n* (%)	Reintervention, *n* (%)	*P*
Surgeon A	94 (93)	7 (7)	NS
Surgeon B	152 (92)	13 (8)	NS
Surgeon C	42 (91)	4 (9)	NS

NS: Nonsignificant

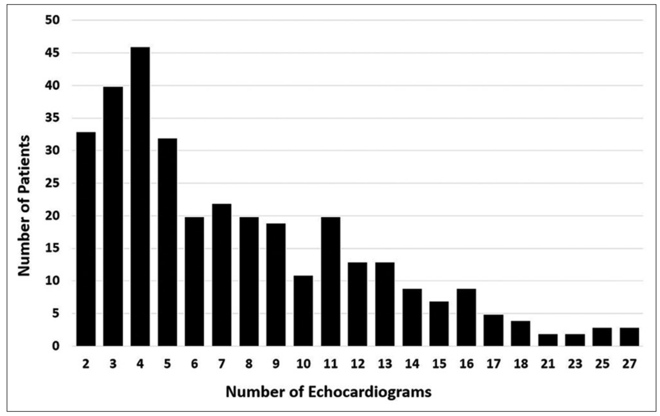

Figure 2: Bar chart displaying the number of performed echocardiograms in relation to the number of individual patients

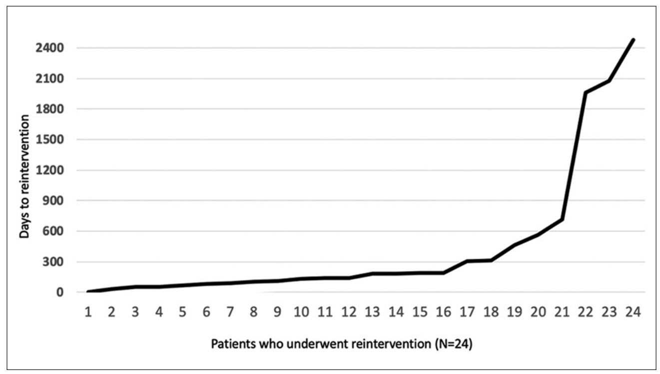

Figure 3: Time for need of a reintervention in the reintervention group showing that of the total of 24 patients, 75% (18 patients) had their reintervention within 1 year after the surgery

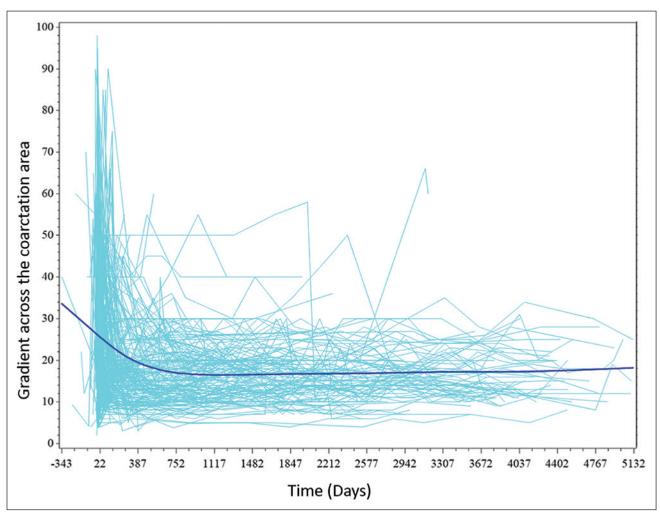

Figure 4: Longitudinal averaged mean line of the peak gradient following surgery for the entire follow up time (15-year). All serial echocardiographic studies (*N* = 2566) for all patients were included. Longitudinal data graphical data display was used respecting the different timing of the echocardiographic measurements. The averaged longitudinal data for the peak gradient showed that most of the changes happen in the 1st 300 days following surgery

hazard modeling by choosing the cut of point that yielded the largest parameter estimate with the least penalizing criterion (Akaike Information Criterion) and with that the cutoff value was 25 mmHg. That is a gradient of 25 or more was associated with a hazard ratio of 5 ($P < 0.0001$).

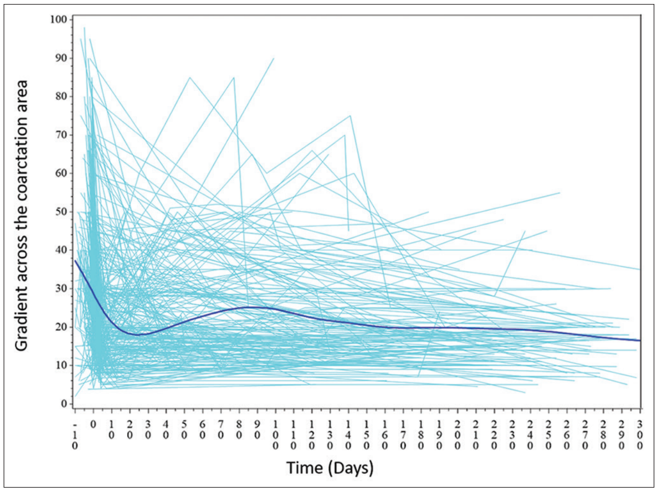

Figure 5: Longitudinal averaged mean line of the peak gradient following surgery for the 1st 300-day following surgery

Comment

Arch obstruction after surgery does not depend on the sort of surgical repair.[7] Residual and recurrent narrowing cannot be easily recognized, and the term recoarctation may be used to characterize both titles. Recoarctation is defined as a peak-to-peak systolic pressure gradient measurement in excess of 20 mm Hg with or without angiographically verifiable narrowing.[8] The recoarctations rates were 11%–17% in babies <1 year and 5.6% in children older than 1 year.[9] In a large sample of cohort study a recoarctation occurred in 23%.[7]

The ePG across the aortic arch as determined by transthoracic cw-Doppler echocardiography is the most common clinical tool to assess the results of a coarctation repair.[10] Ideal results would show laminar flow across the aortic arch with no residual ePG. However, there is almost always an element of flow acceleration and an ePG that could be attributed to arch anatomy or residual narrowing.[11] The value of that residual ePG is ill-defined in the literature. This paper is focused to examine the value of the residual ePGs and their behavior over time and their relationship with the reintervention.

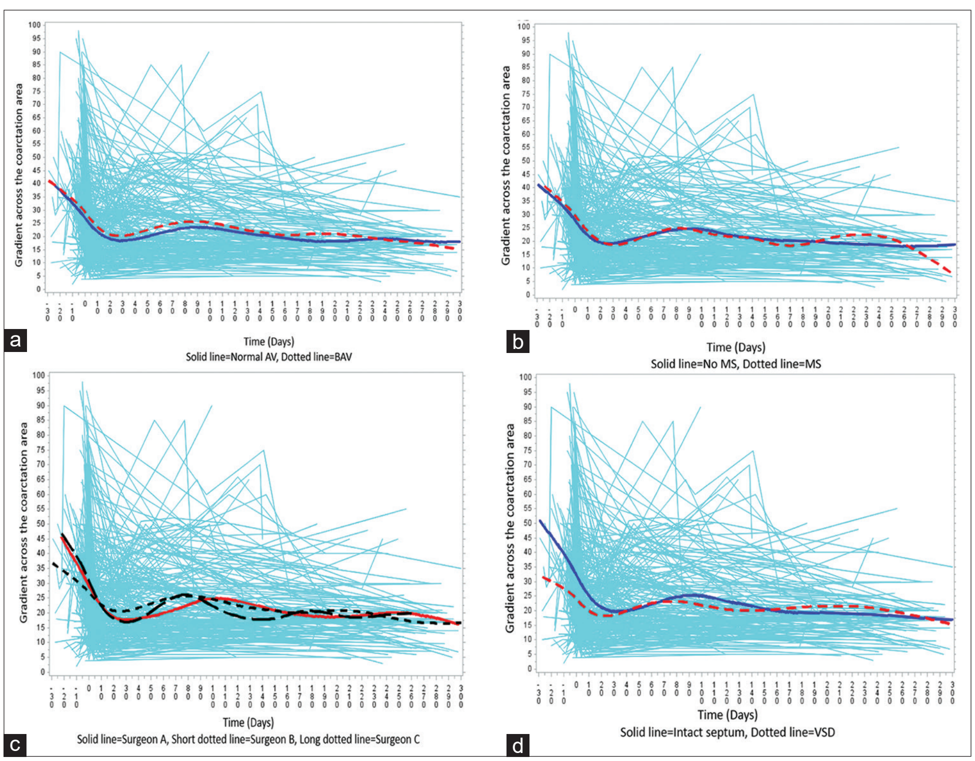

Figure 6: Longitudinal averaged mean line of the peak gradient following surgery for the 1st 300 day following surgery with stratification by BAV, MS, VSD and surgeon. (a) Gradient across the coarctation area over time in a normal Aortic Valve and in the presence of Bicuspid Aortic Valve, (b) Gradient across the coarctation area over time in a the absence of Mitral Stenosis and in the presence of Mitral Stenosis, (c) Gradient across the coarctation area over time in a the presence of different surgeons, (d) Gradient across the coarctation area over time in an intact septum and in the presence of Ventricular Septal Defect. Stratification by the presence of BAV, MS and surgeon did not show any significant differences. Stratification by VSD showed reduced gradient as physiologically expected. BAV: Bicuspid aortic valve, MS: Mitral stenosis, VSD: Ventricular septal defect

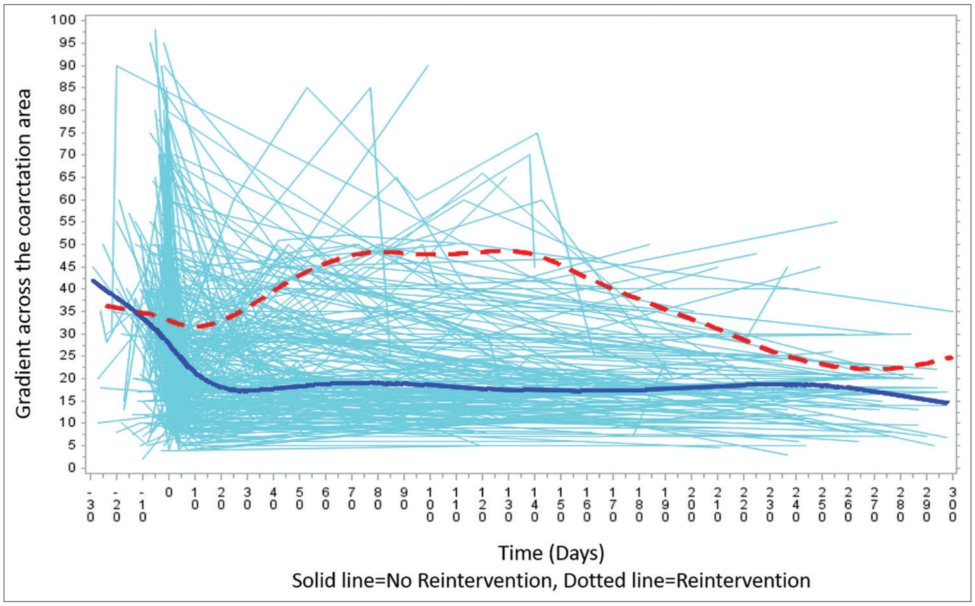

Figure 7: Longitudinal averaged mean line of the peak gradient following surgery for the 1st 300-day following surgery with stratification reintervention. The most notable finding in the stratified longitudinal data display was the rate of drop of the gradient between those who underwent reintervention and those who did not

We included a large number of patients (n = 312) and all their TTE with cw-Doppler measurements that were performed in standardized fashion (n = 2566). The rate of reintervention was 7.7% which is within the range shown in previously published ranges.[12] There was no difference in the ePGs in the presence or absence of associated BAV or MS. It was not surprising to find that the ePGs were less in patients with VSD compared to those without.

Our institutional repair strategy for aortic coarctation constitutes of extended end-to-end anastomosis and the examination of the influence of different surgeons performing the procedure did not show any relation with the reintervention. Furthermore, the effect of the operating surgeon was not significant in predicting the ePG or reintervention in multivariable testing.

The most notable difference in ePGs was seen in the first postoperative TTE. Longitudinal data analysis with stratification based on intervention showed a clear demarcation of the behavior of the ePG. That is if the ePG measured in the first postoperative TTE is high, then it will continue to increase and will necessitate reintervention. Additional statistical techniques were used to determine the best cutoff point of the persisting "high ePG," when it gets higher and when it will allow to predict reintervention. We found that the best cutoff point was an ePG across the aortic arch obtained in the first postoperative echocardiography of 25 mmHg or higher.

Limitations

Due to multiple technicians performing the echocardiographic assessment, an interobserver variability could exist in the analysis using the ePG.

CONCLUSIONS

The ePG acquired in the first postoperative TTE by cw-Doppler is the most important predictor for reinterventions. The presence of a VSD is associated with decreased ePGs. We propose that an ePG in the first postoperative TTE of 25 mmHg or more is a strong predictor for the need of reintervention.

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Conflicts of interest

There are no conflicts of interest.

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